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Formaldehyde

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Canadian Environmental Protection Act, 1999

PRIORITY SUBSTANCES LIST ASSESSMENT REPORT

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Environment Canada
Health Canada

February 2001

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LIST OF ACRONYMS AND ABBREVIATIONS

CAS	Chemical Abstracts Service
CEPA	*Canadian Environmental Protection Act*
CEPA 1999	*Canadian Environmental Protection Act, 1999*
CFD	computational fluid dynamics
CI	confidence interval
CIIT	Chemical Industry Institute of Toxicology
CTV	Critical Toxicity Value
DPX	DNA–protein crosslinking
EEV	Estimated Exposure Value
ENEV	Estimated No-Effects Value
EPA	Environmental Protection Agency
ETS	environmental tobacco smoke
GWP	Global Warming Potential
kg-bw	kilogram body weight
K_{aw}	air/water partition coefficient
K_{oc}	organic carbon/water partition coefficient
K_{ow}	octanol/water partition coefficient
LCL	lower confidence limit
LOEC	Lowest-Observed-Effect Concentration
MDF	medium-density fibreboard
MIR	maximum incremental reactivity
MS	mainstream
NAPS	National Air Pollution Surveillance
NOEC	No-Observed-Effect Concentration
NOEL	No-Observed-Effect Level
NO_x	nitrogen oxides
NPRI	National Pollutant Release Inventory
ODP	Ozone Depletion Potential
OR	odds ratio
PEFR	peak expiratory flow rate
PMR	proportionate mortality ratio
POCP	Photochemical Ozone Creation Potential
PSL	Priority Substances List
RR	relative risk
SIR	standardized incidence ratio
SMR	standardized mortality ratio
SPIR	standardized proportionate incidence ratio
SS	sidestream

TC	Tolerable Concentration
TC_{05}	tumorigenic concentration associated with a 5% increase in tumour incidence over background
UF	urea-formaldehyde
UFFI	urea-formaldehyde foam insulation
VOC	volatile organic compound

SYNOPSIS

In Canada, formaldehyde is used primarily in the production of resins and fertilizers and for a variety of minor uses. The Canadian domestic demand for formaldehyde was 191 000 tonnes in 1996.

Formaldehyde enters the Canadian environment from natural sources (including forest fires) and from direct human sources, such as automotive and other fuel combustion and industrial on-site uses. Secondary formation also occurs, by the oxidation of natural and anthropogenic organic compounds present in air. Although there are no quantitative estimates, releases from natural and secondary sources in Canada are likely greater than direct human releases. However, the highest concentrations measured in the environment occur near anthropogenic sources; these are of prime concern for the exposure of humans and other biota. Motor vehicles, the largest direct human source of formaldehyde in the Canadian environment, released an estimated 11 284 tonnes into the air in 1997. The amount of formaldehyde released into the Canadian environment from industrial processes was 1424 tonnes in 1997.

When formaldehyde is released to or formed in air, most of it will undergo various degradation processes in air, and a very small amount will move into water. When formaldehyde is released into water, it does not move into other media but is broken down in the water. Formaldehyde does not persist in the environment, but its continuous release and formation can result in chronic exposure of biota near sources of release and formation.

Extensive recent data are available for concentrations of formaldehyde in air at industrial, urban, suburban, rural and remote locations in Canada. Data for concentrations in water are limited to surface water from four rivers, effluents from industrial plants and groundwater from three industrial sites and six cemeteries. Environmental toxicity data are available for a wide range of terrestrial and aquatic organisms.

Based on the maximum concentrations measured in air, surface water, effluents and groundwater in Canada, and on the Estimated No-Effects Values derived from experimental data for terrestrial and aquatic biota, formaldehyde is not likely to cause adverse effects on terrestrial or aquatic organisms.

Formaldehyde is not involved in the depletion of stratospheric ozone or in climate change. Because of its photoreactivity and its relatively high concentrations in Canadian cities, formaldehyde plays a role in the photochemical formation of ground-level ozone.

Critical health effects in mammals associated with exposure to formaldehyde occur primarily at the site of first contact (i.e., the respiratory tract following inhalation and the gastrointestinal tract following ingestion) and are related to concentration in the relevant medium, rather than to total intake. The focus of the human health assessment is airborne exposure, due primarily to the lack of representative data on concentrations in media other than air and limited data on effects following ingestion.

Sensory irritation of the eyes and respiratory tract by formaldehyde has been observed consistently in clinical studies and epidemiological surveys in occupational and residential environments. At concentrations higher than those generally associated with sensory irritation, formaldehyde may also contribute to the induction of generally small, reversible effects on lung function.

Following inhalation in laboratory animals, formaldehyde causes degenerative non-neoplastic effects and nasal tumours in rats.

Both sustained cellular proliferation and interaction with genetic material likely contribute to induction of these tumours, and, under similar conditions, formaldehyde is considered to present a carcinogenic hazard to humans.

The majority of the population is exposed to airborne concentrations of formaldehyde less than those associated with sensory irritation. However, in some indoor locations, concentrations may approach those associated with eye and respiratory tract sensory irritation in humans. Based on comparison of risks of cancer estimated on the basis of a biologically motivated case-specific model with calculated exposure in air of the general population in Canada, priority for investigation of options to reduce exposure on the basis of carcinogenicity is considered to be low.

Based on the information available, it is concluded that formaldehyde is not entering the Canadian environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity. Formaldehyde is entering the Canadian environment in a quantity or concentration or under conditions that constitute or may constitute a danger to the environment on which life depends and a danger in Canada to human life or health. Therefore, formaldehyde is considered "toxic" as defined in Section 64 of the *Canadian Environmental Protection Act, 1999* (CEPA 1999).

Formaldehyde contributes to the photochemical formation of ground-level ozone. It is recommended that key sources of formaldehyde be addressed, therefore, as part of management plans for volatile organic chemicals that contribute to the formation of ground-level ozone. While indications are that concentrations currently in air and water are not causing environmental harm to biota, continued and improved monitoring at sites likely to release formaldehyde is desirable, notably with regards to industrial uses for resins and for fertilizers as well as releases from pulp and paper mills.

It is also recommended that continued investigation of options to reduce exposure to formaldehyde in indoor air be considered under the authority of acts other than CEPA 1999 as part of an overall program to reduce exposure to other aldehydes (e.g., acrolein, acetaldehyde) in indoor air deemed to be "toxic" under Paragraph 64(c) of CEPA 1999.

⁂

1.0 INTRODUCTION

The *Canadian Environmental Protection Act, 1999* (CEPA 1999) requires the federal Ministers of the Environment and of Health to prepare and publish a Priority Substances List (PSL) that identifies substances, including chemicals, groups of chemicals, effluents and wastes, that may be harmful to the environment or constitute a danger to human health. The Act also requires both Ministers to assess these substances and determine whether they are "toxic" or capable of becoming "toxic" as defined in Section 64 of the Act, which states:

> ... a substance is toxic if it is entering or may enter the environment in a quantity or concentration or under conditions that
>
> (a) have or may have an immediate or long-term harmful effect on the environment or its biological diversity;
>
> (b) constitute or may constitute a danger to the environment on which life depends; or
>
> (c) constitute or may constitute a danger in Canada to human life or health.

Substances that are assessed as "toxic" as defined in Section 64 may be placed on Schedule I of the Act and considered for possible risk management measures, such as regulations, guidelines, pollution prevention plans or codes of practice to control any aspect of their life cycle, from the research and development stage through manufacture, use, storage, transport and ultimate disposal.

Based on an initial screening of readily accessible information, the rationale for assessing formaldehyde provided by the Ministers' Expert Advisory Panel on the Second Priority Substances List (Ministers' Expert Advisory Panel, 1995) was as follows:

> Canadians are exposed to formaldehyde through its production; its use in the production of resins; in automobile exhaust and cigarette smoke; and through the "off-gassing" of building materials and consumer products including cosmetics and household cleaning agents. Toxicological effects in animals and humans have been observed at levels similar to the concentrations to which the general population may be exposed. Formaldehyde is genotoxic and carcinogenic in rodents and may be carcinogenic in humans. An assessment is needed to determine the potential risk to human health.

Descriptions of the approaches to assessment of the effects of Priority Substances on the environment and human health are available in published companion documents. The document entitled "Environmental Assessments of Priority Substances under the *Canadian Environmental Protection Act*. Guidance Manual Version 1.0 — March 1997" (Environment Canada, 1997a) provides guidance for conducting environmental assessments of Priority Substances in Canada. This document may be purchased from:

Environmental Protection Publications
Environmental Technology Advancement
Directorate
Environment Canada
Ottawa, Ontario
K1A 0H3

It is also available on the Commercial Chemicals Evaluation Branch web site at www.ec.gc.ca/cceb1/ese/eng/esehome.htm under the heading "Guidance Manual." It should be noted that the approach outlined therein has evolved to incorporate recent developments in risk assessment methodology that will be addressed in future releases of the guidance manual for environmental assessments of Priority Substances.

The approach to assessment of effects on human health is outlined in the following publication of the Environmental Health Directorate of Health Canada: "*Canadian Environmental Protection Act* — Human Health Risk Assessment for Priority Substances" (Health Canada, 1994), copies of which are available from:

Environmental Health Centre
Room 104
Health Canada
Tunney's Pasture
Ottawa, Ontario
K1A 0L2

or on the Environmental Health Directorate publications web site (www.hc-sc.gc.ca/ehp/ehd/catalogue/bch.htm). The approach is also described in an article published in the *Journal of Environmental Science and Health — Environmental Carcinogenesis & Ecotoxicology Reviews* (Meek *et al.*, 1994). It should be noted that the approach outlined therein has evolved to incorporate recent developments in risk assessment methodology, which are described on the Environmental Substances Division web site (www.hc-sc.gc.ca/ehp/ehd/bch/env_contaminants/psap/psap.htm) and which will be addressed in future releases of the approach paper for the assessment of effects on human health.

The search strategies employed in the identification of data relevant to assessment of potential effects on the environment (prior to December 1999) and human health (prior to January 1999) are presented in Appendix A. Available Canadian data on sources, use patterns and fate of formaldehyde in the environment have been emphasized. In supporting documentation for this assessment, a report on the health effects of formaldehyde prepared previously by the Bureau of Chemical Hazards, Health Canada (BCH, 1988), was updated. This was based, in part, on a background report compiled by BIBRA Toxicology International (BIBRA, 1994). Review articles were consulted where appropriate. However, all original studies that form the basis for determining whether formaldehyde is "toxic" under CEPA 1999 have been critically evaluated by staff of Environment Canada (entry and environmental exposure and effects) and Health Canada (human exposure and effects on human health).

An Environmental Resource Group was established by Environment Canada to assist in the preparation of the environmental assessment. Members participated in the preparation and review of the environmental sections of the Assessment Report and the environmental supporting document (Environment Canada, 1999a). Members included:

G. Bird, Natural Resources Canada
B. Brownlee, Environment Canada
N. Bunce, University of Guelph
R. Chénier, Environment Canada
T. Currah, OxyChem Durez
T. Dann, Environment Canada
E. Dowdall, Environment Canada
F. Edgecomb, Canadian Plastics Industry Association
M. Eggleton, Environment Canada
G. Granville, Shell Canada Limited
L. Kamboj, Monsanto
R. Keefe, Imperial Oil Limited
G. Rideout, Environment Canada
A. Stelzig, Environment Canada
M. Tushingham, Environment Canada
J. Wittwer, Environment Canada

The environmental assessment was led by R. Chénier and coordinated by A. Bobra (AMBEC Environmental Consultants) on behalf of Environment Canada.

The sections of the Assessment Report relevant to the environmental assessment and the environmental supporting document were reviewed by members of the Environmental Resource Group, as well as by A. Day (Celanese Canada Inc.), D. Mackay (University of Toronto) and P. Makar (Environment Canada).

The content of the health-related sections of this Assessment Report and the supporting documentation (Health Canada, 1999, 2000) was prepared by the following staff of Health Canada:

R. Beauchamp
R.G. Liteplo
M.E. Meek

M. Walker and J. Zielenski, Division of Biostatistics and Research Coordination, Health Canada, and D. Blakey and G. Douglas, Environmental and Occupational Toxicology Division, Health Canada, contributed to the preparation of sections on dose–response analyses for cancer and genotoxicity, respectively.

In the first stage of external review, background sections of the supporting documentation pertaining to human health were reviewed primarily to address adequacy of coverage. Written comments were provided by J. Acquavella (Monsanto Company), S. Felter (Toxicology Excellence for Risk Assessment), O. Hernandez (U.S. Environmental Protection Agency [EPA]), R. Keefe (Imperial Oil Limited), N. Krivanek (Dupont Haskell Laboratory), J. Martin (consultant) and F. Miller (Chemical Industry Institute of Toxicology [CIIT]) (June 1997).

In 1996, a government–private Steering Committee was formed in the United States to develop a model for dose–response analyses for formaldehyde that takes into account as much of the biological database on formaldehyde as possible. This partnership involved primarily the CIIT and the U.S. EPA. Toxicology Excellence for Risk Assessment, commissioned by the Formaldehyde Epidemiology, Toxicology, and Environmental Group, Inc., also participated, preparing sections of draft documentation related to hazard assessment. Health Canada joined this partnership later, contributing by organizing, in collaboration with the U.S. EPA, an external peer review workshop and revising some sections of the draft documentation related to hazard assessment (in particular, those addressing epidemiological data).

The product of this joint effort was a draft document entitled "Formaldehyde: Hazard Characterization and Dose–Response Assessment for Carcinogenicity by the Route of Inhalation" (CIIT, 1999). This report, which was developed primarily by CIIT (with input from J. Overton, U.S. EPA), was reviewed at an external peer review workshop of the following invitees, convened by Health Canada and the U.S. EPA on March 18–20, 1998, in Ottawa, Ontario (Health Canada, 1998):

B. Allen, RAS Associates
M. Andersen, ICF Kaiser Engineering (*Chair*)
D. Blakey, Health Canada
A. Dahl, Lovelace Respiratory Research Institute
D. Gaylor, U.S. Food and Drug Administration
J. Harkema, Michigan State University
D. Jacobson-Kram, MA BioServices
D. Krewski, Health Canada
R. Maronpot, National Institute of Environmental Health Sciences
G. Marsh, University of Pittsburgh
J. Siemiatycki, Institut Armand-Frappier
J. Ultman, Pennsylvania State University

Written comments were also provided by S. Moolgavkar (Fred Hutchinson Cancer Research Center).

Following the workshop, the report was revised to reflect comments of the external reviewers and recirculated; written comments on the subsequently revised draft were submitted by all members of the external review panel (November 1998). The final draft (dated September 28, 1999) (CIIT, 1999) was reviewed by the Chair of the workshop (M. Andersen) to ensure that comments had been adequately addressed (Andersen, 1999).

In this assessment, the outcome of this collaborative exercise and additional data on non-cancer effects and routes of exposure other than ingestion have been considered in the context of the approach to assessment of "toxic" under Paragraph 64(c) of CEPA 1999.

R. Vincent, Environmental Toxicology Division, Health Canada, provided comments on the Assessment Report. Accuracy of reporting, adequacy of coverage and defensibility of conclusions with respect to hazard characterization and dose–response analyses were considered in written review by M. Andersen (Colorado State University), V. Feron, (TNO-Nutrition and Food Research Institute) and J. Swenberg (University of North Carolina).

The health-related sections of the Assessment Report were reviewed and approved by the Healthy Environments and Consumer Safety Branch Risk Management meeting of Health Canada.

The entire Assessment Report was reviewed and approved by the Environment Canada/Health Canada CEPA Management Committee.

A draft of the Assessment Report was made available for a 60-day public comment period (July 22 to September 20, 2000) (Environment Canada and Health Canada, 2000). Following consideration of comments received, the Assessment Report was revised as appropriate. A summary of the comments and responses is available on the Internet at:

www.ec.gc.ca/cceb1/eng/final/index_e.html

The text of the Assessment Report has been structured to address environmental effects initially (relevant to determination of "toxic" under Paragraphs 64(a) and (b)), followed by effects on human health (relevant to determination of "toxic" under Paragraph 64(c)).

Copies of this Assessment Report are available upon request from:

Inquiry Centre
Environment Canada
Main Floor, Place Vincent Massey
351 St. Joseph Blvd.
Hull, Quebec
K1A 0H3

or on the Internet at:
www.ec.gc.ca/cceb1/eng/final/index_e.html

Unpublished supporting documentation on the environmental assessment (Environment Canada, 1999a) or health assessment (BCH, 1988; Health Canada, 1998, 1999, 2000; Andersen, 1999; CIIT, 1999), which presents additional information, is available upon request from:

Commercial Chemicals Evaluation
Branch
Environment Canada
14th Floor, Place Vincent Massey
351 St. Joseph Blvd.
Hull, Quebec
K1A 0H3

or

Environmental Health Centre
Room 104
Health Canada
Tunney's Pasture
Ottawa, Ontario
K1A 0L2

⁂

2.0 Summary of Information Critical to Assessment of "Toxic" under CEPA 1999

2.1 Identity and physical/chemical properties

Pure formaldehyde is also known as methanal, methylene oxide, oxymethylene, methylaldehyde, oxomethane, formic aldehyde and methylene glycol. Its Chemical Abstracts Service (CAS) number is 50-00-0. The molecular formula is CH_2O.

At room temperature, formaldehyde is a colourless gas with a pungent, irritating odour. It is highly reactive, readily undergoes polymerization, is highly flammable and can form explosive mixtures in air. It decomposes at temperatures above 150°C. Formaldehyde is readily soluble in water, alcohols and other polar solvents. In aqueous solutions, formaldehyde hydrates and polymerizes and can exist as methylene glycol, polyoxymethylene and hemiformals. Solutions with high concentrations (>30%) of formaldehyde become turbid as the polymer precipitates (WHO, 1989). As a reactive aldehyde, formaldehyde can undergo a number of self-association reactions, and it can associate with water to form a variety of chemical species with properties different from those of the pure monomolecular substance. These associations tend to be most prevalent at high concentrations of formaldehyde, when molecules have an increased opportunity to associate with other like species. Partition coefficients of most pure organic substances such as benzene or hexane reflect the properties of the individual monomolecular species at all concentrations — namely, they do not self-associate. This is not the case for formaldehyde, and it is therefore not advisable to use property data at high concentrations to estimate properties under dilute conditions. For example, the common practice of calculating the air/water partition coefficient (K_{aw}) from solubility and vapour pressure can be invalid for substances such as formaldehyde. The most environmentally relevant and meaningful properties, such as the octanol/water partition coefficient (K_{ow}), K_{aw}, the organic carbon/water partition coefficient (K_{oc}), etc., should be measured at low concentrations. Extrapolation from concentrations exceeding percent levels should be avoided, and thus any use of structure–property relationships and inter-property correlations (such as K_{ow} and solubility) should be examined critically for validity (Bobra and Mackay, 1999).

Values reported for the physical and chemical properties of formaldehyde are given in Table 1.

Pure formaldehyde is not available commercially but is sold as 30–50% (by weight) aqueous solutions. Formalin (37% CH_2O) is the most common solution. Methanol or other substances are usually added to the solution as stabilizers to reduce the intrinsic polymerization of formaldehyde (WHO, 1989; Environment Canada, 1995). In solid form, formaldehyde is marketed as trioxane, $(CH_2O)_3$, and its polymer paraformaldehyde, with 8–100 units of formaldehyde (WHO, 1989).

2.2 Entry characterization

2.2.1 Production, importation, exportation and use

Formaldehyde is produced commercially by the catalytic air oxidation of methanol (Environment Canada, 1985; Kroschwitz, 1991). In Canada, about 222 000 tonnes of formaldehyde were produced in 1996. In the same year, approximately 7600 tonnes of formaldehyde were imported, and more than 30 000 tonnes of

TABLE 1 Physical and chemical properties of formaldehyde reported in literature[1]

Property	Range of reported values[2]
Molecular weight (g/mol)	30.03
Melting point (°C)	–118 to –92
Boiling point (°C, 101.3 kPa)	–21 to –19
Vapour pressure (calculated) (Pa, at 25°C)	516 000
Water solubility (mg/L, at 25°C)[3]	400 000 to 550 000
Henry's law constant (Pa·m^3/mol, 25°C)	2.2×10^{-2} to 3.4×10^{-2}
Log octanol/water partition coefficient (log K_{ow})	–0.75 to 0.35
Log organic carbon/water partition coefficient (log K_{oc})	0.70 to 1.57

[1] Because of polymerization and other reactions, care should be taken in interpreting or using reported values. See also text.

[2] Includes experimental and calculated values from Hansch and Leo (1979, 1981); Karickhoff *et al.* (1979); Kenaga and Goring (1980); Weast (1982–1983); Verschueren (1983); Perry and Green (1984); Dean (1985); U.S. EPA (1985); Betterton and Hoffmann (1988); Deneer *et al.* (1988); Howard (1989); Sangster (1989); Zhou and Mopper (1990); Mackay *et al.* (1995); Staudinger and Roberts (1996).

[3] Water solubility of a chemical is defined as the maximum amount of the chemical that will dissolve in water at a specified temperature, pressure and pH. Results such as 1 220 000 mg/L (Dean, 1985) and 1.0×10^6 mg/L (DMER and AEL, 1996) have been quoted. These values are pseudo-solubilities, since solutions become turbid as the polymer precipitates at concentrations of approximately 55% and greater.

formaldehyde were exported (Environment Canada, 1997c).

Total Canadian domestic consumption of formaldehyde was reported at about 191 000 tonnes for 1996 (Environment Canada, 1997c). Formaldehyde is used predominantly in the synthesis of resins, with urea-formaldehyde (UF) resins, phenolic-formaldehyde resins, pentaerythritol and other resins accounting for about 92% of Canadian consumption. About 6% of uses were related to fertilizer production, while 2% was used for various other purposes, such as preservatives and disinfectants (Environment Canada, 1997c). Formaldehyde can be used in a variety of industries, including the medical, detergent, cosmetic, food, rubber, fertilizer, metal, wood, leather, petroleum and agricultural industries (WHO, 1989), and as a hydrogen sulfide scavenger in oil operations (Tiemstra, 1989).

In Canada, formaldehyde is acceptable for use in non-aerosol cosmetics provided the concentration does not exceed 0.2% (BND, 1994). Formaldehyde is included in the Cosmetic Notification Hot List maintained by Health Canada's Product Safety Bureau with the recommendation to limit its concentration in cosmetics to less than 0.3%, except for fingernail hardeners, for which a maximum concentration of 5% applies (Richardson, 1999).

Approximately 80% of the slow-release fertilizer market is based on UF-containing products (ATSDR, 1999; HSDB, 1999).

In the agriculture industry, formaldehyde has been used as a fumigant, as a preventative for mildew and spelt in wheat and for rot in oats. It has also been used as a germicide and fungicide for plants and vegetables and as an insecticide for destroying flies and other insects. In Canada, there are currently 59 pest control products containing formaldehyde registered under the *Pest Control Products Act*. Formaldehyde is present as a formulant in 56 of these products, at concentrations ranging from 0.002% to 1% by weight. Formaldehyde is an active ingredient in the remaining three products, at concentrations ranging from 2.3% to 37% in the commercially available products (Moore, 2000). Pesticidal uses are not considered in this assessment because they are regulated by the *Pest Control Products Act*.

Section 15 of Health Canada's *Food and Drugs Act* allows up to 2 ppm (i.e., 2 mg/kg) formaldehyde in maple syrup resulting from the use of paraformaldehyde to deter bacterial growth in the tap holes of maple trees (Feeley, 1996). However, such use has not been registered in Canada since 1990 (Smith, 2000).

2.2.2 *Sources and releases*

Formaldehyde is formed primarily by the combustion of organic materials and by a variety of natural and anthropogenic activities. Secondary formation of formaldehyde occurs in the atmosphere through the oxidation of natural and anthropogenic volatile organic compounds (VOCs) in the air. While there are no reliable estimates for releases from natural sources and for secondary formation, these may be expected to be much larger than direct emissions from anthropogenic activities. However, highest concentrations have been measured near key anthropogenic sources, such as automotive and industrial emissions (see below).

2.2.2.1 Natural sources

Formaldehyde occurs naturally in the environment and is the product of many natural processes. It is released during biomass combustion, such as forest and brush fires (Howard, 1989; Reinhardt, 1991). In water, it is also formed by the irradiation of humic substances by sunlight (Kieber *et al*., 1990).

As a metabolic intermediate, formaldehyde is present at low levels in most living organisms (WHO, 1989; IARC, 1995). Studies have found it to be emitted by bacteria, algae, plankton and vegetation (Hellebust, 1974; Zimmermann *et al*., 1978; Eberhardt and Sieburth, 1985; Yamada and Matsui, 1992; Nuccio *et al*., 1995).

2.2.2.2 Anthropogenic sources

Anthropogenic sources of formaldehyde include direct sources such as fuel combustion, industrial on-site uses and off-gassing from building materials and consumer products.

Although formaldehyde is not present in gasoline, it is a product of incomplete combustion. All internal combustion engines have the potential to produce it. The amount generated depends primarily on the composition of the fuel, the type of engine, the emission control applied, the operating temperature and the age and state of repair of the vehicle. Therefore, emission rates are variable (Environment Canada, 1999a).

Based on data for 1997 reported to the National Pollutant Release Inventory (NPRI), on-road motor vehicles are the largest direct source of formaldehyde released into the Canadian environment. The amount estimated by modelling to have been released in 1997 from on-road motor vehicles was 11 284 tonnes (Environment Canada, 1999b). While Environment Canada (1999b) did not distinguish between gasoline-powered and diesel-powered vehicles, it has been estimated, based on emission data from these vehicles, that they account for about 40% and 60% of on-road automotive releases, respectively. Aircraft emitted an estimated 1730 tonnes, and the marine sector released about 1175 tonnes (Environment Canada, 1999b). Data on releases from on-road vehicles were estimated by modelling (Mobile 5C model), using assumptions outlined in Environment Canada (1996). It can be expected that the rates of releases of formaldehyde from automotive sources have changed and will continue to change; many current and planned modifications to automotive emission control technology and gasoline quality would lead to decreases in the releases of formaldehyde and other VOCs (Environment Canada, 1999b).

Other anthropogenic combustion sources (covering a range of fuels from wood to plastics) include wood-burning stoves, fireplaces, furnaces, power plants, agricultural burns, waste incinerators, cigarette smoking and the cooking of food (Jermini *et al.*, 1976; Kitchens *et al.*, 1976; Klus and Kuhn, 1982; Ramdahl *et al.*, 1982; Schriever *et al.*, 1983; Lipari *et al.*, 1984; WHO, 1989; Walker and Cooper, 1992; Baker, 1994; Guski and Raczynski, 1994). Cigarette smoking in Canada is estimated to produce less than 84 tonnes per year, based on estimated emission rates (WHO, 1989) and a consumption rate of approximately 50 billion cigarettes per year (Health Canada, 1997). Canadian coal-based electricity generating plants are estimated to emit 0.7–23 tonnes per year, based on U.S. emission factors (Lipari *et al.*, 1984; Sverdrup *et al.*, 1994), the high heating value of fuel and Canadian coal consumption in 1995 (Rose, 1998). A gross estimate of formaldehyde emissions from municipal, hazardous and biomedical waste in Canada is 10.6 tonnes per year, based on measured emission rates from one municipal incinerator in Ontario (Novamann International, 1997; Environment Canada, 1999a).

Industrial releases of formaldehyde can occur at any stage during the production, use, storage, transport or disposal of products with residual formaldehyde. Formaldehyde has been detected in emissions from chemical manufacturing plants (Environment Canada, 1997c,d, 1999a), pulp and paper mills, forestry product plants (U.S. EPA, 1990; Fisher *et al.*, 1991; Environment Canada, 1997c, 1999a; O'Connor and Voss, 1997), tire and rubber plants (Environment Canada, 1997b), petroleum refining and coal processing plants (IARC, 1981; U.S. EPA, 1993), textile mills, automotive manufacturing plants and the metal products industry (Environment Canada, 1999a).

NPRI data for 1997 indicated total environmental releases from 101 facilities of 1423.9 tonnes, with reported releases to different media as follows: 1339.3 tonnes to air, 60.5 tonnes to deep-well injection, 19.4 tonnes to surface water and 0 tonnes to soil. Largest emissions to air were reported from Weyerhaeuser Canada Ltd. in Edson, Alberta (121.5 tonnes), and Drayton Valley, Alberta (111.7 tonnes). Only four plants reported releases of formaldehyde to surface water, in quantities of 13.3 tonnes (Abitibi-Consolidated, La Baie, Quebec), 4.1 tonnes (Abitibi Consolidated, Grand-Mère, Quebec), 1.6 tonnes (Tembec Inc., Témiscaming, Quebec) and 0.4 tonnes (Grant Forest Products Corp., Englehart, Ontario). Formaldehyde disposed of through deep-well injection is not considered to interact with biologically active soil strata. From 1979 to 1989, about 76.9 tonnes of formaldehyde were spilled or released to the environment as a result of 35 reported incidents (NATES, 1996).

Releases of formaldehyde to groundwater from embalming fluids in bodies buried in cemeteries are expected to be very small based on groundwater samples and the estimated loading rates of six cemeteries in Ontario (Chan *et al.*, 1992).

Formaldehyde has been detected in the off-gassing of formaldehyde products such as wood panels, latex paints, new carpets, textile products and resins. While emission rates have been estimated for some of these sources, there are insufficient data for estimating total releases (Little *et al.*, 1994; NCASI, 1994; Environment Canada, 1995).

Regulatory and voluntary initiatives have been directed at the control of emissions from building materials and furnishings, since these are recognized as the major sources of elevated concentrations of formaldehyde in indoor air. Urea-formaldehyde foam insulation (UFFI) was banned from use in Canada in 1980. Voluntary standards have been established to limit the emission of formaldehyde from particleboard (ANSI A208.1-1993) and medium-density fibreboard (MDF) (ANSI A208.2-1994). According to information provided by the Composite Panel Association (formerly the National Particleboard Association and the Canadian Particleboard Association), a dramatic reduction in the emission rates of formaldehyde from composite wood products has been achieved through the use of low-emitting resins, chemical scavengers and improved manufacturing control

(Tardif, 1998). The Canadian Carpet Institute has established a voluntary carpet emission guideline of 0.05 mg/m^2 per hour (Piersol, 1995).

2.2.2.3 Secondary formation

Formaldehyde is formed in the troposphere by the photochemical oxidation of many types of organic compounds, including naturally occurring compounds, such as methane (WHO, 1989; U.S. EPA, 1993) and isoprene (Tanner *et al.*, 1994), and pollutants from mobile and stationary sources, such as alkanes, alkenes (e.g., ethene, propene), aldehydes (e.g., acetaldehyde, acrolein) and alcohols (e.g., allyl alcohol, methanol, ethanol) (U.S. EPA, 1985; Atkinson *et al.*, 1989, 1993; Grosjean, 1990a,b, 1991a,b,c; Skov *et al.*, 1992; Grosjean *et al.*, 1993a,b, 1996a,b; Bierbach *et al.*, 1994; Kao, 1994).

Given the diversity and abundance of formaldehyde precursors in urban air, secondary atmospheric formation frequently exceeds direct emissions from combustion sources, especially during photochemical air pollution episodes, and it may contribute up to 70–90% of the total atmospheric formaldehyde (Grosjean, 1982; Grosjean *et al.*, 1983; Lowe and Schmidt, 1983). In California, Harley and Cass (1994) estimated that photochemical formation was more important than direct emissions in Los Angeles during the summertime days studied; in winter or at night and early morning, direct emissions can be more important. This was also observed in Japan, where the concentrations of formaldehyde in the central mountainous region were not associated directly with motor exhaust but rather with the photochemical oxidation of anthropogenic pollutants occurring there through long-range transport (Satsumabayashi *et al.*, 1995).

2.3 Exposure characterization

2.3.1 Environmental fate

The sections below summarize the available information on the distribution and fate of formaldehyde released into the environment. More detailed fate information is provided in Environment Canada (1999a).

2.3.1.1 Air

Formaldehyde emitted to air primarily reacts with photochemically generated hydroxyl (OH) radicals in the troposphere or undergoes direct photolysis (Howard *et al.*, 1991; U.S. EPA, 1993). Minor fate processes include reactions with nitrate (NO_3) radicals, hydroperoxyl (HO_2) radicals, hydrogen peroxide (H_2O_2), ozone (O_3) and chlorine (Cl_2) (U.S. EPA, 1993). Small amounts of formaldehyde may also transfer into rain, fog and clouds or be removed by dry deposition (Warneck *et al.*, 1978; Zafiriou *et al.*, 1980; Howard, 1989; Atkinson *et al.*, 1990; U.S. EPA, 1993).

Reaction with the hydroxyl radical is considered to be the most important photooxidation process, based on the rate constants and the concentrations of the reactants (Howard *et al.*, 1991; U.S. EPA, 1993). Factors influencing the atmospheric lifetime of formaldehyde, such as time of day, intensity of sunlight, temperature, etc., are mainly those affecting the availability of hydroxyl and nitrate radicals (U.S. EPA, 1993). The atmospheric half-life of formaldehyde, based on hydroxyl radical reaction rate constants, is calculated to be between 7.1 and 71.3 hours (Atkinson, 1985; Atkinson *et al.*, 1990). Products that can be formed from hydroxyl radical reaction include water (H_2O), formic acid (HCOOH), carbon monoxide (CO) and the hydroperoxyl/formaldehyde adduct (HCO_3) (Atkinson *et al.*, 1990).

Photolysis can take two pathways. The dominant pathway produces stable molecular hydrogen and carbon monoxide. The other pathway produces the formyl (HCO) radical and a hydrogen atom (Lowe *et al.*, 1980), which react quickly with oxygen to form the hydroperoxyl radical and carbon monoxide. Under many conditions, the radicals from formaldehyde photolysis are the most important net source of smog generation (U.S. EPA, 1993). When the rates of these reactions are combined with estimates of actinic radiance, the estimated half-life of formaldehyde due to photolysis is 1.6 hours in the lower troposphere at a solar zenith angle of 40° (Calvert *et al.*, 1972). A half-life of 6 hours was measured based on simulated sunlight (Lowe *et al.*, 1980).

The nighttime destruction of formaldehyde is expected to occur by the gas-phase reaction with nitrate radicals (NRC, 1981); this tends to be more significant in urban areas, where the concentration of the nitrate radical is higher than in rural areas (Altshuller and Cohen, 1964; Gay and Bufalini, 1971). A half-life of 160 days was calculated using an average atmospheric nitrate radical concentration typical of a mildly polluted urban centre (Atkinson *et al.*, 1990), while a half-life of 77 days was estimated based on measured rate constants (Atkinson *et al.*, 1993). Nitric acid (HNO_3) and formyl radical have been identified as products of this reaction. They react rapidly with atmospheric oxygen to produce carbon monoxide and hydroperoxyl radicals, which can react with formaldehyde to form formic acid. However, because of this rapid back-reaction, the reaction of nitrate radicals with formaldehyde is not expected to be a major loss process under tropospheric conditions.

Overall half-lives for formaldehyde in air can vary considerably under different conditions. Estimations for atmospheric residence time in several U.S. cities ranged from 0.3 hours under conditions typical of a rainy winter night to 250 hours under conditions typical of a clear summer night (assuming no reaction with hydroperoxyl radicals) (U.S. EPA, 1993). During the daytime, under clear-sky conditions, the residence time is determined primarily by its reaction with the hydroxyl radical. Photolysis accounted for only 2–5% of the removal.

Given the generally short daytime residence times for formaldehyde, there is limited potential for long-range transport of this compound. However, in cases where organic precursors are transported long distances, secondary formation of formaldehyde may occur far from the actual anthropogenic sources of the precursors (Tanner *et al.*, 1994).

Because of its high solubility in water, formaldehyde will transfer into clouds and precipitation. A washout ratio (concentration in rain/concentration in air) of 73 000 at 25°C is estimated by Atkinson (1990). Gas-phase organic compounds that have a washout ratio of greater than 105 are generally estimated to be efficiently rained out (ARB, 1993). The washout ratio suggests that the wet deposition (removal of gases and particles by precipitation) of formaldehyde could be significant as a tropospheric loss process (Atkinson, 1989). However, Zafiriou *et al.* (1980) estimated that rainout was responsible for removing only 1% of formaldehyde produced in the atmosphere by the oxidation of methane. Warneck *et al.* (1978) showed that washout is important only in polluted regions. Nevertheless, it is expected that wet deposition can lead to a somewhat shorter tropospheric lifetime of formaldehyde than that calculated from gas-phase processes alone.

2.3.1.2 Water

In water, formaldehyde is rapidly hydrated to form a glycol ($CH_2(OH)_2$). Equilibrium almost totally favours the glycol (Dong and Dasgupta, 1986); less than 0.04% by weight of unhydrated formaldehyde is found in highly concentrated solutions (Kroschwitz, 1991). In surface water or groundwater, formaldehyde can undergo biodegradation (U.S. EPA, 1985; Howard, 1989). Incorporated into atmospheric water, formaldehyde or its hydrate can undergo oxidation.

Formaldehyde is degraded by various mixed microbial cultures obtained from sludges and sewage (Kitchens *et al.*, 1976; Verschueren, 1983; U.S. EPA, 1985). Formaldehyde in lake water decomposed in approximately 30 hours under aerobic conditions at 20°C and in approximately 48 hours under anaerobic conditions (Kamata, 1966). Howard *et al.* (1991) estimated half-lives of 24–168 hours in surface water and 48–336 hours in groundwater based on scientific judgment and estimated aqueous aerobic biodegradation half-lives.

When incorporated from air into cloud water, fog water or rain, formaldehyde can react with aqueous hydroxyl radicals in the presence of oxygen to produce formic acid, water and hydroperoxide (aqueous). The formaldehyde glycol can also react with ozone (Atkinson *et al.*, 1990).

2.3.1.3 Sediment

Due to its low K_{oc} and high water solubility, formaldehyde is not expected to significantly sorb to suspended solids and sediments from water. Biotic and abiotic degradation are expected to be the significant environmental fate processes in sediment (U.S. EPA, 1985; Howard, 1989).

2.3.1.4 Soil

Formaldehyde is not expected to adsorb to soil particles to a great degree and would be considered mobile in the soil, based on its estimated K_{oc}. According to Kenaga (1980), compounds with a K_{oc} of <100 are considered to be moderately mobile. Formaldehyde can be transported to surface water through runoff and to groundwater as a result of leaching. Parameters other than K_{oc} affecting its leaching to groundwater include the soil type, the amount and frequency of rainfall, the depth of the groundwater and the extent of degradation of formaldehyde. Formaldehyde is susceptible to degradation by various soil microorganisms (U.S. EPA, 1985). Howard *et al.* (1991) estimated a soil half-life of 24–168 hours, based on estimated aqueous aerobic biodegradation half-lives.

2.3.1.5 Biota

In view of the very low bioconcentration factor of 0.19, based on a log K_{ow} of 0.65 (Veith *et al.*, 1980; Hansch and Leo, 1981), formaldehyde is not expected to bioaccumulate. No bioconcentration was observed in fish or shrimp (Stills and Allen, 1979; Hose and Lightner, 1980). No significant aquatic magnification in the food chain is predicted from the model calculations and empirical observations of Thomann (1989).

2.3.1.6 Environmental distribution

Fugacity modelling was carried out to provide an overview of key reaction, intercompartment and advection (movement out of a system) pathways for formaldehyde and its overall distribution in the environment. A steady-state, non-equilibrium model (Level III fugacity model) was run using the methods developed by Mackay (1991) and Mackay and Paterson (1991). Assumptions, input parameters and results are presented in Mackay *et al.* (1995) and Environment Canada (1999a).

Based on its physical-chemical properties, Level III fugacity modelling indicates that when formaldehyde is continuously discharged into one medium, most of it can be expected to be found in that medium (Mackay *et al.*, 1995; DMER and AEL, 1996). However, given the uncertainties relating to use of pseudo-solubility, hydration in water, and the complex atmospheric formation and degradation processes for formaldehyde, quantitative estimates of mass distribution are not considered reliable for formaldehyde.

2.3.2 Environmental concentrations

2.3.2.1 Air

2.3.2.1.1 Ambient air

Available sampling and analytical methodologies are sufficiently sensitive to detect formaldehyde in most samples of ambient (outdoor) air in Canada. Formaldehyde was detected (detection limit 0.05 µg/m^3) in 3810 of 3842 24-hour samples from rural, suburban and urban areas, collected at 16 sites in six provinces surveyed from August 1989 to August 1998 (Environment Canada, 1999a). Concentrations ranged from below the detection limit (0.05 µg/m^3) to a maximum of 27.5 µg/m^3 for eight urban sites (Montréal, Quebec [two sites]; Ottawa, Ontario; Windsor, Ontario [two sites]; Toronto, Ontario; Winnipeg, Manitoba; Vancouver, B.C.), to a maximum of

12.03 µg/m^3 for two suburban sites (Saint John, New Brunswick; Montréal, Quebec), to a maximum of 9.11 µg/m^3 for two rural sites considered to be affected by urban and/or industrial influences (L'Assomption, Quebec; Simcoe, Ontario) and to a maximum of 9.88 µg/m^3 for four rural sites considered to be regionally representative (Kejimkujik Park, Nova Scotia; Mount Sutton, Quebec; St. Anicet, Quebec; Egbert, Ontario). Long-term (1 month to 1 year) mean concentrations for these sites ranged from 0.78 to 8.76 µg/m^3. The single highest 24-hour concentration measured was 27.5 µg/m^3, obtained for an urban sample collected from Toronto, Ontario, on August 8, 1995. The mean concentration for six 24-hour measurements made at this site during the 30-day period from July 14 to August 12 was 22.15 µg/m^3. Pooled monthly mean concentrations of formaldehyde determined from data in Canada's National Air Pollution Surveillance (NAPS) program for suburban and urban sites in Canada between 1990 and 1998 are highest between June and August (Health Canada, 2000).

Concentrations of formaldehyde were measured in 96 air samples (12- to 25-hour) collected from the roofs of buildings at four sites in urban, residential and industrial areas of Prince Rupert, B.C., during 1994 and 1995. Concentrations ranged from 0.08 to 14.7 µg/m^3 (detection limit 0.03 µg/m^3). Reported averages ranged from 0.73 to 3.94 µg/m^3 (SEAM Database, 1996).

Quarterly mean concentrations of formaldehyde in outdoor air during the period from 1990 to 1998 were calculated for two suburban (i.e., in Montréal and Vancouver) and two urban (i.e., in Ottawa and Toronto) NAPS sites and examined for temporal trends. There is no evidence that concentrations of formaldehyde were systematically increasing or decreasing at these sites over this 9-year period (Health Canada, 2000).

Formaldehyde was also measured in 108 6-hour samples collected 4 times daily from August 1 to 28, 1993, at Chebogue Point, Nova Scotia. Concentrations ranged from less than 0.6 µg/m^3 to approximately 4.2 µg/m^3 (detection limit not specified) (Tanner *et al.*, 1994). This area was assumed to be affected not only by local sources but also by air masses transporting precursors from the northeastern United States.

Atmospheric measurements made in 1992 during the dark winter and sunlit spring of an extremely remote site at Alert, Nunavut, ranged from 0.04 to 0.84 µg/m^3 on a 5-minute basis (detection limit 0.04 µg/m^3), with a mean of 0.48 µg/m^3 (De Serves, 1994).

Concentrations of formaldehyde were determined in air near a forest product plant. The maximum 24-hour average concentrations for March–June 1995, July–September 1995 and October 1995 – March 1996 were 3.01, 1.71 and 4.40 µg/m^3, respectively (detection limit not specified) (Environment Canada, 1997c).

2.3.2.1.2 Indoor air

Few recent data were identified concerning concentrations of formaldehyde in residential indoor air in Canada. In contrast, large numbers of measurements of formaldehyde in the indoor air of Canadian homes were made during the 1970s and 1980s (Government of Canada, 1982) in response to concerns about emissions of formaldehyde from UFFI. These older data, reflecting higher concentrations of formaldehyde in the residential indoor air of "complaint" homes, were not considered to be representative of the concentrations in indoor air to which the general population is currently exposed.

Data concerning concentrations of formaldehyde in residential indoor air from seven studies conducted in Canada between 1989 and 1995 were examined (Health Canada, 2000). Despite differences in sampling mode and duration (i.e., active sampling for 24 hours or passive sampling for 7 days), the distributions of concentrations were similar in five of the studies. The median, arithmetic mean, 95th percentile and

99th percentile concentrations of the pooled data (n = 151 samples) from these five studies were 30, 36, 85 and 116 µg/m^3, respectively (Health Canada, 2000). Similar concentrations have been measured in non-workplace indoor air in other countries.

Concurrent 24-hour measurements in outdoor air and indoor air of Canadian residences were available from some of these studies. Average concentrations of formaldehyde were an order of magnitude higher in indoor air than in outdoor air, indicating the presence of indoor sources of formaldehyde and confirming similar findings in other countries (WHO, 1989; ATSDR, 1999). Information concerning the presence of environmental tobacco smoke (ETS) in the homes sampled was available from some of these studies; however, there was no clear indication that concentrations of formaldehyde were greater in homes where ETS was present. Acetaldehyde, rather than formaldehyde, is the most abundant carbonyl compound in mainstream (MS) and sidestream (SS) cigarette smoke. Based on data from the United States and elsewhere, ETS does not increase concentrations of formaldehyde in indoor air, except in areas with high rates of smoking and minimal rates of ventilation (Godish, 1989; Guerin *et al.*, 1992).

The available Canadian data were inadequate to permit the assessment of the extent of contributions from other combustion sources (e.g., woodstoves, vehicles in attached garages, etc.) or other potential sources (e.g., furniture, building materials) to the measured concentrations of formaldehyde in indoor air.

2.3.2.2 Water

2.3.2.2.1 Drinking water

Representative data concerning concentrations in drinking water in Canada were not available. The concentration of formaldehyde in drinking water is likely dependent upon the quality of the raw source water and purification steps utilized (Krasner *et al.*, 1989). Ozonation may slightly increase the levels of formaldehyde in drinking water, but subsequent purification steps may attenuate these elevated concentrations (Huck *et al.*, 1990). Elevated concentrations have been measured in U.S. houses equipped with polyacetal plumbing elbows and tees. Normally, an interior protective coating prevents water from contacting the polyacetal resin (Owen *et al.*, 1990). However, if routine stress on the supply lines results in a break or fracture of the coating, water may contact the resin directly. The resultant concentrations of formaldehyde in the water are largely determined by the residence time of the water in the pipes. Owen *et al.* (1990) estimated that at normal water usage rates in occupied dwellings, the resulting concentration of formaldehyde in water would be about 20 µg/L. In general, concentrations of formaldehyde in drinking water are expected to be less than 100 µg/L (WHO, 1989; IARC, 1995).

2.3.2.2.2 Surface water

Concentrations of formaldehyde in raw water from the North Saskatchewan River were measured at the Rossdale drinking water treatment plant in Edmonton, Alberta. Concentrations between March 1989 and January 1990 averaged 1.2 µg/L, with a peak value of 9.0 µg/L. These concentrations were influenced by climatological events such as spring runoff, major rainfall events and the onset of winter, as evidenced by concentration increases during spring runoff and major rainfall and concentration decreases (<0.2 µg/L) following river freeze-up (Huck *et al.*, 1990).

Anderson *et al.* (1995) measured formaldehyde concentrations in the raw water of three drinking water treatment pilot plants in Ontario. The study included three distinct types of surface waters, covering a range of characteristics and regional influences: a moderately hard waterway with agricultural impacts (Grand River at Brantford), a soft, coloured river (Ottawa River at Ottawa) and a river with moderate values for most parameters, typical of the Great Lakes waterways (Detroit

River at Windsor). Concentrations were less than the detection limit (1.0 µg/L) and 8.4 µg/L in raw water samples collected on December 2, 1993, and February 15, 1994, respectively, from the Detroit River. In the Ottawa River, concentrations were below the detection limit (1.0 µg/L) in three profiles taken between April 12 and June 7, 1994. In the Grand River, a mean concentration of 1.1 µg/L was obtained for seven sampling dates between May 11 and June 21, 1994.

2.3.2.2.3 Effluent

Formaldehyde is not routinely measured as part of most industrial permitting or monitoring of effluent releases. Recent follow-up with individual plants reporting releases indicated that plants that had previously released effluents to surface waters now release to municipal wastewater systems or divert their effluents to activated sludge treatment prior to release into the environment, thereby reducing or eliminating releases of formaldehyde. The highest reported concentration from one of the four plants reporting releases for 1997 (Environment Canada, 1999b) was a 1-day mean of 325 µg/L, with a 4-day mean of 240 µg/L (Environment Canada, 1999a).

2.3.2.2.4 Groundwater

Extensive monitoring of groundwater from a site of production and use of formaldehyde included 10 samples in which formaldehyde concentrations were below the detection limit (50 µg/L) and 43 samples with concentrations ranging from 65 to 690 000 µg/L (mean of two duplicates) from November 1991 to February 1992 (Environment Canada, 1997c). Data had been collected as part of a monitoring program to delineate the boundaries of groundwater contamination at the facility and were used to design a groundwater containment and recovery system. Formaldehyde was not detected in samples taken from outside the contaminated zone. Waste ponds associated with the formaldehyde releases are no longer in service and have been capped, and the wastewater is now treated in an effluent treatment unit (Environment Canada, 1999a).

Quarterly analyses of five monitoring wells on the property of a plant that produces UF resins were carried out during 1996–1997. Concentrations ranged from below the detection limit (50 µg/L) to 8200 µg/L, with an overall median of 100 µg/L. Concentrations for different wells indicated little dispersion from wells close to the source of contamination (Environment Canada, 1997c).

Samples from eight monitoring wells at a fibreglass insulation plant were reported to have concentrations ranging from below detection (5 µg/L) to 190 µg/L on March 24, 1997. Groundwater data from 1996 indicate concentrations from below the detection limit (0.5–5.4 µg/L) up to 120 µg/L. However, review of the analytical methods used indicates that these results may be unreliable (Environment Canada, 1997c).

Groundwater samples were collected from wells downstream from six cemeteries in Ontario. They contained formaldehyde concentrations of 1–30 µg/L (detection limit not specified). These values could be overestimates, as a blank sample was found to contain 7.3 µg/L (Chan *et al.*, 1992).

2.3.2.2.5 Atmospheric water

While no data are available in Canada, concentrations of formaldehyde in rain, snow, fog and cloud water have been measured in other countries. Rain concentrations ranged from 0.44 µg/L (near Mexico City) to 3003 µg/L (during the burning season in Venezuela). Mean concentrations ranged from 77 µg/L (in Germany) to 321 µg/L (during the non-burning season in Venezuela). In snow, formaldehyde concentrations ranged from 18 to 901 µg/L in California. A mean snow concentration of 4.9 µg/L is reported for Germany. In fog water, concentrations of 480–17 027 µg/L have been measured in the Po valley, Italy, with a mean of 3904 µg/L (see Environment Canada, 1999a).

2.3.2.3 Sediment

No data were identified on concentrations of formaldehyde in sediments in Canada.

2.3.2.4 Soil

Concentrations in soil were measured at manufacturing plants that use phenol/formaldehyde resins. At a plywood plant, six soil samples collected in 1991 contained formaldehyde concentrations of 73–80 mg/kg, with a mean of 76 mg/kg (detection limit not specified) (Alberta Environmental Protection, 1996). At a fibreglass insulation plant, formaldehyde was not detected (detection limit 0.1 mg/kg) in soil samples collected in 1996 from six depths at four industrial areas on-site. Formaldehyde was also not detected in samples taken from a non-industrial site 120 km away from the plant.

2.3.2.5 Biota

No data were identified on concentrations of formaldehyde in Canadian biota.

2.3.2.6 Food

There have been no systematic investigations of levels of formaldehyde in a range of foodstuffs as a basis for estimation of population exposure (Health Canada, 2000). Although formaldehyde is a natural component of a variety of foodstuffs (WHO, 1989; IARC, 1995), monitoring has generally been sporadic and source-directed. Available data suggest that the highest concentrations of formaldehyde naturally occurring in foods (i.e., up to 60 mg/kg) are in some fruits (Möhler and Denbsky, 1970; Tsuchiya *et al.*, 1975) and marine fish (Rehbein, 1986; Tsuda *et al.*, 1988).

Formaldehyde develops post-mortem in marine fish and crustaceans, from the enzymatic reduction of trimethylamine oxide to formaldehyde and dimethylamine (Sotelo *et al.*, 1995). While formaldehyde may be formed during the ageing and deterioration of fish flesh, high levels do not accumulate in the fish tissues, due to subsequent conversion of the formaldehyde formed to other chemical compounds (Tsuda *et al.*, 1988). However, formaldehyde accumulates during the frozen storage of some fish species, including cod, pollack and haddock (Sotelo *et al.*, 1995). Formaldehyde formed in fish reacts with protein and subsequently causes muscle toughness (Yasuhara and Shibamoto, 1995), which suggests that fish containing the highest levels of formaldehyde (e.g., 10–20 mg/kg) may not be considered palatable as a human food source. No data regarding the formaldehyde content of freshwater fish, marine fish or shellfish in Canada were identified.

Higher concentrations of formaldehyde (i.e., up to 800 mg/kg) have been reported in fruit and vegetable juices in Bulgaria (Tashkov, 1996); however, it is not clear if these elevated levels arise during processing. Formaldehyde is used in the sugar industry to inhibit bacterial growth during juice production (ATSDR, 1999). In a study conducted by Agriculture Canada, concentrations of formaldehyde were higher in sap from maple trees that had been implanted with paraformaldehyde to deter bacterial growth in tap holes (Baraniak *et al.*, 1988). The resulting maple syrup contained concentrations up to 14 mg/kg, compared with less than 1 mg/kg in syrup from untreated trees.

In other processed foods, the highest concentrations have been reported in the outer layer of smoked ham (Brunn and Klostermeyer, 1984) and in some varieties of Italian cheese, where formaldehyde is permitted for use under regulation as a bacteriostatic agent (Restani *et al.*, 1992). Hexamethylenetetramine, a complex of formaldehyde and ammonia that decomposes slowly to its constituents under acid conditions, has been used as a food additive in fish products such as herring and caviar in the Scandinavian countries (Scheuplein, 1985).

Concentrations of formaldehyde in a variety of alcoholic beverages ranged from 0.04 to 1.7 mg/L in Japan (Tsuchiya *et al.*, 1994) and from 0.02 to 3.8 mg/L in Brazil (de Andrade *et al.*, 1996). In earlier work conducted in Canada, Lawrence and Iyengar (1983) compared levels of formaldehyde in bottled and canned cola soft drinks (7.4–8.7 mg/kg) and beer (0.1–1.5 mg/kg) and concluded that there was no significant increase in the formaldehyde content of canned beverages due to the plastic inner coating of the metal containers. Concentrations of 3.4 and 4.5 mg/kg in brewed coffee and 10 and 16 mg/kg in instant coffee were reported in the United States (Hayashi *et al.*, 1986). These concentrations reflect the levels in the beverages as consumed.

Data from several studies indicate that low concentrations of formaldehyde may be present in various prepared foods and that various cooking activities may contribute to the elevated levels of formaldehyde sometimes present in indoor air (Health Canada, 2000). In recent work from the United States, the emission rate of formaldehyde from meat charbroiling over a natural gas-fired grill in a commercial facility was higher (i.e., 1.38 g/kg of meat cooked) than emission rates of all other VOCs measured except for ethylene (Schauer *et al.*, 1999).

Formaldehyde is used in the animal feed industry, where it is added to ruminant feeds to improve handling characteristics. The food mixture contains less than 1% formaldehyde, and animals may ingest as much as 0.25% formaldehyde in their diet (Scheuplein, 1985). Formalin has been added as a preservative to skim milk fed to pigs in the United Kingdom (Florence and Milner, 1981) and to liquid whey (from the manufacture of cheddar and cottage cheeses) fed to calves and cows in Canada. Maximum concentrations in the milk of cows fed whey with the maximum level of formalin tested (i.e., 0.15%) were up to 10-fold greater (i.e., 0.22 mg/kg) than levels in milk from control cows fed whey without added formalin (Buckley *et al.*, 1986, 1988). In a more recent study, the concentrations of formaldehyde in commercial 2% milk and in fresh milk from cows fed on a typical North American dairy total mixed diet were determined. Concentrations in the fresh milk (i.e., from Holstein cows, morning milking) ranged from 0.013 to 0.057 mg/kg, with a mean concentration (n = 18) of 0.027 mg/kg, while concentrations in processed milk (i.e., 2% milk fat, partly skimmed, pasteurized) ranged from 0.075 to 0.255 mg/kg, with a mean concentration (n = 12) of 0.164 mg/kg. The somewhat higher concentrations in the commercial 2% milk were attributed to processing technique, packaging and storage, but these factors were not assessed further (Kaminski *et al.*, 1993).

The degree to which formaldehyde in various foods is bioavailable following ingestion is not known.

2.3.2.7 Consumer products

Formaldehyde and formaldehyde derivatives are present in a wide variety of consumer products (Preuss *et al.*, 1985) to protect the products from spoilage by microbial contamination. Formaldehyde is used as a preservative in household cleaning agents, dishwashing liquids, fabric softeners, shoe-care agents, car shampoos and waxes, carpet cleaning agents, etc. (WHO, 1989). Levels of formaldehyde in hand dishwashing liquids and liquid personal cleansing products available in Canada are less than 0.1% (w/w) (McDonald, 1996).

Formaldehyde has been used in the cosmetics industry in three principal areas: preservation of cosmetic products and raw materials against microbial contamination, certain cosmetic treatments such as hardening of fingernails, and plant and equipment sanitation (Jass, 1985). Formaldehyde is also used as an antimicrobial agent in hair preparations, lotions (e.g., suntan lotion and dry skin lotion), makeup and mouthwashes and is also present in hand cream, bath products, mascara and eye makeup, cuticle softeners, nail creams, vaginal deodorants and shaving cream (WHO, 1989; ATSDR, 1999).

Some preservatives are formaldehyde releasers. The release of formaldehyde upon their decomposition is dependent mainly on temperature and pH. Information on product categories and typical concentrations for chemical products containing formaldehyde and formaldehyde releasers was obtained from the Danish Product Register Data Base (PROBAS) by Flyvholm and Andersen (1993). Industrial and household cleaning agents, soaps, shampoos, paints/lacquers and cutting fluids comprised the most frequent product categories for formaldehyde releasers. The three most frequently registered formaldehyde releasers were bromonitropropanediol, bromonitrodioxane and chloroallylhexaminium chloride (Flyvholm and Andersen, 1993).

Formaldehyde is present in the smoke resulting from the combustion of tobacco products. Estimates of emission factors for formaldehyde (e.g., µg/cigarette) from MS and SS smoke and from ETS have been determined by a number of different protocols for cigarettes in several countries, including Canada.

A range of MS smoke emission factors from 73.8 to 283.8 µg/cigarette was reported for 26 U.S. brands, which included non-filter, filter and menthol cigarettes of various lengths (Miyake and Shibamoto, 1995). Differences in concentrations reflect differences in tobacco type and brand. More recent information is available from the British Columbia Ministry of Health from tests conducted on 11 brands of Canadian cigarettes. MS smoke emission factors ranged from 8 to 50 µg/cigarette when tested under standard conditions (British Columbia Ministry of Health, 1998).

Levels of formaldehyde are higher in SS smoke than in MS smoke. Guerin *et al.* (1992) reported that popular commercial U.S. cigarettes deliver approximately 1000–2000 µg formaldehyde per cigarette in their SS smoke. Schlitt and Knöppel (1989) reported a mean (n = 5) formaldehyde content of 2360 µg/cigarette in the SS smoke from a single brand in Italy. Information from the British Columbia Ministry of Health from tests conducted on 11 brands of Canadian cigarettes indicates that emission factors from SS smoke ranged from 368 to 448 µg/cigarette (British Columbia Ministry of Health, 1998).

Emission factors for toxic chemicals from ETS, rather than from MS or SS smoke, have also been determined. This is in part due to concerns that emission factors for SS smoke may be too low for reactive chemicals such as formaldehyde, due to losses in the various apparati used to determine SS smoke emission factors. Daisey *et al.* (1994) indicated that ETS emission factors for formaldehyde from six U.S. commercial cigarettes ranged from 958 to 1880 µg/cigarette, with a mean of 1310 ± 349 µg/cigarette. Data concerning emission factors for formaldehyde from ETS produced by Canadian cigarettes were not identified.

2.3.2.8 Clothing and fabrics

Formaldehyde-releasing agents provide crease resistance, dimensional stability and flame retardance for textiles and serve as binders in textile printing (Priha, 1995). Durable-press resins or permanent-press resins containing formaldehyde have been used on cotton and cotton/polyester blend fabrics since the mid-1920s to impart wrinkle resistance during wear and laundering. Hatch and Maibach (1995) identified nine major resins used. These differ in formaldehyde-releasing potential during wear and use.

Priha (1995) indicated that formaldehyde-based resins, such as UF resin, were once more commonly used for crease resistance treatment; more recently, however, better finishing agents with lower formaldehyde release have been developed. Totally formaldehyde-free crosslinking agents are now available, and some countries have legally limited the formaldehyde content of textile products. In 1990, the percentage of durable-press fabric manufactured in the United States finished with resins rated as having high formaldehyde release was 27%, about one-half the percentage in 1980, according to Hatch and Maibach (1995). It has been reported that the average level contained by textiles made in the United States is approximately 100–200 ppm free formaldehyde (Scheman *et al.*, 1998).

Piletta-Zanin *et al.* (1996) studied the presence of formaldehyde in moist baby toilet tissues and tested 10 of the most frequently sold products in Switzerland. One product contained more than 100 ppm (i.e., µg/g), five products contained between 30 and 100 ppm, and the remaining four products contained less than 30 ppm formaldehyde.

2.3.2.9 Building materials

The emission of formaldehyde from building materials has long been recognized as a significant source of the elevated concentrations of formaldehyde frequently measured in indoor air. Historically, the most important indoor source among the many materials used in building and construction has been UFFI, which is produced by the aeration of a mixture of UF resin and an aqueous surfactant solution containing a curing catalyst (Meek *et al.*, 1985). UFFI was banned from use in Canada in 1980 and in the United States in 1982, although the U.S. ban was subsequently overturned.

Pressed wood products (i.e., particleboard, MDF and hardwood plywood) are now considered the major sources of residential formaldehyde contamination (Godish, 1988; Etkin, 1996). Pressed wood products are bonded with UF resin; it is this adhesive portion that is responsible for the emission of formaldehyde into indoor air. The emission rate of formaldehyde is strongly influenced by the nature of the material. Generally, release of formaldehyde is highest from newly made wood products. Emissions then decrease over time, to very low rates, after a period of years (Godish, 1988).

Concentrations of formaldehyde in indoor air are primarily determined by source factors that include source strength, loading factors and the presence of source combinations (Godish, 1988). The best currently available approach to evaluating the source strength of indoor materials and products is to test their emission rates (Tucker, 1990). Emission rates of formaldehyde from pressed wood products determined by emission chamber testing in Canada (Figley and Makohon, 1993; Piersol, 1995), the United Kingdom (Crump *et al.*, 1996) and the United States (Kelly *et al.*, 1999) are now typically less than 0.3 mg/m^2 per hour (Health Canada, 2000).

Formaldehyde release from pressed wood materials is greater in mobile homes than in conventional housing, since mobile homes typically have higher loading ratios (e.g., exceeding 1 m^2/m^3) of these materials. In addition, mobile homes can have minimal ventilation, are minimally insulated and are often situated in exposed sites subject to temperature extremes (Meyer and Hermanns, 1985).

The use of scavengers (e.g., urea) to chemically remove unreacted formaldehyde while the curing process is taking place has been investigated as a control measure. Other reactants could be used to chemically modify the formaldehyde to a non-toxic derivative or convert it to a non-volatile reaction product. Work has also been done on resin sealants to effectively seal the resin and prevent the residual formaldehyde from escaping (Tabor, 1988). Surface coatings and treatments (e.g., paper and vinyl decorative laminates) can significantly affect an original material's off-gassing characteristics and in some cases can result in an order of magnitude reduction in the emission rates of formaldehyde from pressed wood products (Figley and Makohon, 1993; Kelly *et al.*, 1999). On the other hand, high emissions of formaldehyde during the curing of some commercially available conversion varnishes (also known as acid-catalyst varnishes) have been reported. An initial formaldehyde emission rate of 29 mg/m^2 per hour was determined for one product (McCrillis *et al.*, 1999).

Emission rates of formaldehyde from carpets and carpet backings, vinyl floorings and wall coverings are now generally less than 0.1 mg/m^2 per hour (Health Canada, 2000).

2.4 Effects characterization

2.4.1 Ecotoxicology

Below, a brief summary is presented of the most sensitive organisms for the terrestrial and aquatic endpoints. More extensive description of available data on environmental effects is provided in several reviews (NRC, 1982; WHO, 1989; RIVM, 1992) and in the databases given in Appendix A.

2.4.1.1 Terrestrial organisms

The most sensitive effect for terrestrial organisms resulting from exposure to formaldehyde in air was an increase in the growth of shoots, but not of roots, of the common bean (*Phaseolus vulgaris*) after exposure to average measured concentrations of 78, 128, 239 and 438 µg/m^3 in air (day: 25°C, 40% humidity; night: 14°C, 60% humidity) for 7 hours per day, 3 days per week, for 4 weeks, beginning at the appearance of the first macroscopic floral bud, 20 days after emergence (Mutters *et al.*, 1993). Although the authors concluded that there were no short-term harmful effects, it has been suggested that an imbalance between shoot and root growth may increase a plant's vulnerability to environmental stresses such as drought, because the root system may not be large enough to provide water and nutrients for healthy plant growth (Barker and Shimabuku, 1992). Other sensitive effects on terrestrial vegetation include a significant reduction of the pollen tube length of lily (*Lilium longiflorum*) following a 5-hour exposure to 440 µg/m^3 in air; total inhibition of pollen tube elongation occurred at 1680 µg/m^3 (Masaru *et al.*, 1976). A 5-hour exposure to 840 µg/m^3 caused mild atypical signs of injury in alfalfa (*Medico sativa*), but no injury to spinach (*Spinacia oleracea*), beets (*Beta vulgaris*) or oats (*Avena sativa*) (Haagen-Smit *et al.*, 1952).

Effects on plants were also studied following exposure to formaldehyde in fog water. Seedlings of winter wheat (*Triticum aestivum*), aspen (*Populus tremuloides*), rapeseed (*Brassica rapa*) and slash pine (*Pinus elliotti*) were exposed to formaldehyde concentrations of 0, 9000 or 27 000 µg/L in fog for 4.5 hours per night, 3 nights per week, for 40 days. Based on an unspecified Henry's law constant, calculated corresponding atmospheric gas-phase formaldehyde concentrations were 0, 18 and 54 µg/m^3, respectively. In rapeseed grown in the formaldehyde fog, significant ($p \leq 0.1$) reductions in leaf area, leaf dry weight, stem dry weight, flower number and number of mature siliques (seed pods that produce seed) were observed compared with control plants. The slash pine showed a significant increase in needle and stem growth. No effects were observed in the wheat or aspen at test concentrations (Barker and Shimabuku, 1992).

Formaldehyde is known to be an effective disinfectant that kills microorganisms such as bacteria, viruses, fungi and parasites at relatively high concentrations (WHO, 1989). Exposure to 2 ppm (2400 µg/m^3) gaseous formaldehyde for 24 hours killed 100% of spores from cultures of various species of *Aspergillus*, *Scopulariopsis* and *Penicillium crustosum* (Dennis and Gaunt, 1974). In a fumigation study, the death rate of spores of *Bacillus globigii* increased from low to high with formaldehyde concentrations ranging from 50 000 to 400 000 µg/m^3, respectively. Humidity (>50%) appeared to shorten the delay before death (Cross and Lach, 1990).

For terrestrial invertebrates, nematodes in peat were killed by fumigation applications of 370 g/L formaldehyde solutions at a rate of 179 mL/m^3 (66 g/m^3) (Lockhart, 1972). Solutions of 1% and 5% formalin (37% formaldehyde) destroyed the eggs and affected larvae, respectively, of the cattle parasites *Ostertagia ostertagi* and *Cooperia oncophora* in liquid cow manure (Persson, 1973).

No acute or chronic toxicity data were identified for wild mammals, birds, reptiles or terrestrial invertebrates. Effects on laboratory mammals are presented in Section 2.4.3.

2.4.1.2 Aquatic organisms

Data on the aquatic toxicity of formaldehyde are numerous. The most sensitive aquatic effects identified were observed for marine algae. Formaldehyde concentrations of 0.1 and 1 mg/L in water caused 40–50% mortality after 96 hours in day-old zygotes of *Phyllospora comosa*, a brown marine macroalga endemic to southeastern Australia. Total (100%) mortality resulted from exposures to 100 mg/L for 24 hours and 10 mg/L for 96 hours. The 96-hour No-Observed-Effect Concentration (NOEC) and Lowest-Observed-Effect Concentration (LOEC) (percent mortality not specified) of 7-day-old embryos of the same species were reported as 1 and 10 mg/L, respectively, indicating that older organisms are more tolerant (Burridge *et al.*, 1995a). Concentrations of 0.1, 1 and 10 mg/L also reduced germination and growth rates of the zygotes and embryos (Burridge *et al.*, 1995b).

Freshwater algae may be slightly more tolerant of formaldehyde, based on a cell multiplication inhibition test (Bringmann and Kühn, 1980a). The premise of this test is that the number of cells in a test culture free from dissolved toxic substances will exceed that of a contaminated culture after a certain period with otherwise identical conditions and nutrient supplies. The number of cells in suspension can be measured turbidimetrically and is expressed as the extinction of primary light at 578 nm for a 10-mm layer of cells. A mean extinction of ≥3% lower than that of controls is described as the toxicity threshold. In this study, the green alga, *Scenedesmus quadricauda*, was exposed to various dilutions of formalin (35% CH_2O w/w) for 7 days (shaken once a day). The toxicity threshold was 0.9 mg formaldehyde/L (2.5 mg formalin/L) (Bringmann and Kühn, 1980a).

Other freshwater microorganisms were similarly sensitive in analogous cell multiplication studies. A 48-hour toxicity threshold (5% below average cell counts of controls) of 1.6 mg formaldehyde/L (4.5 mg formalin/L, 35% CH_2O w/w) was determined for the saprozoic flagellate protozoan, *Chilomona paramaecium* (Bringmann *et al.*, 1980), and a 72-hour toxicity threshold (≥3% inhibition of cell multiplication, 25°C) of 7.7 mg/L (22 mg formalin/L, 35% CH_2O w/w) was reported for the protozoan, *Entosiphon sulcatum* (Bringmann and Kühn, 1980b). For bacteria, the 16-hour toxicity threshold (≥3% inhibition of cell multiplication) was 4.9 mg formaldehyde/L (14 mg formalin/L, 35% CH_2O w/w) for *Pseudomonas putida* (Bringmann and Kühn, 1980a), and a 25-minute EC_{50} (light emission inhibition) of 2.5 mg formaldehyde/L (242 µM formalin, 37% CH_2O w/w) was observed in the *Photobacterium phosphoreum* Microtox test (Chou and Que Hee, 1992).

The sensitivity of freshwater invertebrates to formaldehyde varies widely. The seed shrimp, *Cypridopsis* sp., appears to be the most sensitive, with a 96-hour EC_{50} (immobility) of 0.36 mg formaldehyde/L (1.05 µL formalin/L, 37% CH_2O w/w). The snail, *Helisoma* sp., bivalve, *Corbicula* sp., freshwater prawn, *Palaemonetes hadiakensis*, and backswimmer, *Notonecta* sp., have 96-hour EC_{50} values (immobility, delayed response to tactile stimuli) of 32, 43, 160 and 287 µg/L (93, 126, 465 and 835 µL formalin/L, 37% CH_2O w/w), respectively, assuming 1 µL formalin/L = 0.34 mg formaldehyde/L (Bills *et al.*, 1977). Reported 24-hour LC_{50} values for *Daphnia magna* range from 2 to 1000 mg/L (WHO, 1989).

Formaldehyde toxicity is variable for fish as well. The most sensitive freshwater fish were fingerlings of striped bass (*Roccus saxatilis*). Reardon and Harrell (1990) found 96-hour LC_{50} values of 1.8, 5.0, 5.7 and 4.0 mg/L (4.96, 13.52, 15.48 and 10.84 mg formalin/L, 37% CH_2O w/w) in water with 0, 5, 10 and 15‰ salinity, respectively. These values were calculated from nominal test concentrations using probit analyses. Salinity may have an effect on the tolerance of striped bass to formaldehyde. Although the fish had been acclimated to water with a salinity of 10–30‰ prior to testing, they were most tolerant of formaldehyde in isosmotic medium (9–10‰). Since controls were not affected by the changes in salinity, there may be a compounded effect of chemical and environmental (e.g., salinity) interaction on fish survival. Wellborn (1969) reported a 96-hour LC_{50} of 6.7 mg/L for striped bass under static conditions. Other short-term (3- to 96-hour) LC_{50}s of between 10 and 10 000 mg/L were reported for 19 species and three life stages of freshwater fish (U.S. EPA, 1985; WHO, 1989). In some studies, formaldehyde caused disruption of normal gill function (Reardon and Harrell, 1990).

The only data identified for marine fish were for the juvenile marine pompano (*Trachinotus carolinus*), with 24-, 48- and 72-hour LC_{50} values of 28.8, 27.3 and 25.6 mg formaldehyde/L (78.0, 73.7 and 69.1 mg formalin/L, assumed to contain 37% CH_2O), respectively, in 30‰ salinity. Salinity (10, 20, 30‰) did not significantly affect the tolerance of fish to formaldehyde (Birdsong and Avault, 1971).

The sensitivity of amphibians to formaldehyde is similar to that of fish. The lowest 24-, 48- and 72-hour LC_{50} values were 8.4, 8.0 and 8.0 mg/L, respectively, for larvae of the leopard frog (*Rana pipiens*). Tadpoles of bullfrogs appear more tolerant, with 24-, 48- and 72-hour LC_{50} values of 20.1, 17.9 and 17.9 mg/L, respectively. Larvae of the toad, *Bufo* sp., had 72-hour LC_{50} and LC_{100} values of 17.1 and 19.0 mg/L, respectively (Helms, 1964). Mortality (13–100%) in tadpoles of the Rio Grande leopard frog (*Rana berlandieri*) was observed after 24 hours in formaldehyde (9.2–30.5 mg/L) (Carmichael, 1983). A NOEC (mortality) of 6.0 mg/L was reported.

2.4.2 Abiotic atmospheric effects

The potential for formaldehyde to contribute to the depletion of stratospheric ozone, to climate change or to formation of ground-level ozone was examined.

Since formaldehyde is not a halogenated compound, its Ozone Depletion Potential (ODP) is 0, and it will therefore not contribute to the depletion of stratospheric ozone (Bunce, 1996).

Gases involved in climate change strongly absorb infrared radiation of wavelengths between 7 and 13 µm, enabling them to trap and re-radiate the Earth's thermal radiation (Wang *et al.*, 1976; Ramanathan *et al.*, 1985). Worst-case calculations were made to determine if formaldehyde has the potential to contribute to climate change (Bunce, 1996), assuming it has the same infrared absorption strength as the reference compound, CFC-11. The Global Warming Potential (GWP) was calculated to be 3.2×10^{-4} (relative to the reference compound CFC-11, which has a GWP of 1), based on the following formula:

$$GWP = (t_{formaldehyde}/t_{CFC\text{-}11}) \times (M_{CFC\text{-}11}/M_{formaldehyde}) \times (S_{formaldehyde}/S_{CFC\text{-}11})$$

where:

- $t_{formaldehyde}$ is the lifetime of formaldehyde (4.1×10^{-3} years),
- $t_{CFC\text{-}11}$ is the lifetime of CFC-11 (60 years),
- $M_{CFC\text{-}11}$ is the molecular weight of CFC-11 (137.5 g/mol),
- $M_{formaldehyde}$ is the molecular weight of formaldehyde (30 g/mol),
- $S_{formaldehyde}$ is the infrared absorption strength of formaldehyde (2389/cm^2 per atmosphere, default), and
- $S_{CFC\text{-}11}$ is the infrared absorption strength of CFC-11 (2389/cm^2 per atmosphere).

Since this estimate for the GWP is much less than 1% of that of the reference compound, it is unlikely that formaldehyde could contribute significantly to climate change (Bunce, 1996).

The contribution of VOCs to the formation of ground-level ozone, and the resulting contribution to smog formation, is a complex process and has been studied extensively. The terms reactivity, incremental reactivity and photochemical ozone formation potential denote the ability of an organic compound in the atmosphere to influence the formation of ozone

(Paraskevopoulos *et al.*, 1995). Estimates of reactivity of a substance depend on the definition and method of calculation of the reactivity, the VOC/NO_X ratio, the age of the air mass, the chemical mechanisms in the model, the chemical composition of the hydrocarbon mixture into which the VOC is emitted, the geographical and meteorological conditions of the airshed of interest (including temperature and intensity and quality of light) and the extent of dilution (Paraskevopoulos *et al.*, 1995).

The Photochemical Ozone Creation Potential (POCP) is one of the simpler indices of the potential contribution of an organic compound to the formation of ground-level ozone, based on the rate of reaction of the substance with the hydroxyl radical relative to ethene (CEU, 1995). Ethene, a chemical that is considered to be important in ozone formation, has an assigned POCP value of 100. The POCP for formaldehyde was estimated to be 105 relative to ethene, using the following formula (Bunce, 1996):

$$POCP = (k_{formaldehyde}/k_{ethene}) \times (M_{ethene}/M_{formaldehyde}) \times 100$$

where:

- $k_{formaldehyde}$ is the rate constant for the reaction of formaldehyde with OH radicals (9.6×10^{-12} cm^3/mol per second),
- k_{ethene} is the rate constant for the reaction of ethene with OH radicals (8.5×10^{-12} cm^3/mol per second),
- M_{ethene} is the molecular weight of ethene (28.1 g/mol), and
- $M_{formaldehyde}$ is the molecular weight of formaldehyde (30 g/mol).

Various published reactivity values for formaldehyde and other selected VOCs are presented by Paraskevopoulos *et al.* (1995). The use of a maximum incremental reactivity (MIR) scale has been recommended by Carter (1994) as optimal when applied to the wide variety of conditions where ozone is sensitive to VOCs, being fairly robust to the choices of scenarios used to derive it. Experimental data indicate that for formaldehyde, direct radical formation from its photolysis is the key factor leading to net contribution to ozone formation under conditions of low reactive organic gas to NO_X ratios (Carter *et al.*, 1995).

Recently, formaldehyde was one of the VOCs identified in the Canadian 1996 NO_X/VOC Science Assessment as part of the Multi-Stakeholder NO_X/VOC Science Program (Dann and Summers, 1997). Based on air measurements taken at nine urban and suburban sites in Canada from June to August from 1989 to 1993, formaldehyde was ranked 16th of the most abundant non-methane hydrocarbon and carbonyl species. Based on these measurements and on an MIR value of 4.39 mol ozone/mol carbon, formaldehyde represented approximately 7.8% of the total volatile organic carbon reactivity and was ranked 4th when sorted by the total volatile organic carbon reactivities. Total volatile organic carbon reactivity denotes the ability of organic compounds to contribute to the formation of ozone.

Therefore, based on its reactivity and the concentrations encountered in Canada, formaldehyde is likely to play a role in the photochemical formation of ground-level ozone in urban areas in Canada.

2.4.3 Experimental animals and in vitro

Information on non-neoplastic effects associated with the repeated inhalation or oral exposure of laboratory animals to formaldehyde is summarized in Tables 2 and 3, respectively.

2.4.3.1 Acute toxicity

Reported LC_{50}s in rodents for the inhalation of formaldehyde range from 493 to 984 mg/m^3 (WHO, 1989). For rats and guinea pigs, oral LD_{50}s of 800 and 260 mg/kg-bw have been reported (WHO, 1989). Acute exposure of animals to elevated concentrations of formaldehyde (e.g., >120 mg/m^3) produces dyspnea, vomiting, hypersalivation, muscle spasms and death (WHO, 1989). Alterations in

TABLE 2 Summary of non-neoplastic effect levels (inhalation) for formaldehyde

Protocol	Results		Critical effect [*comments*]	Reference
	NO(A)EL	LO(A)EL		
Short-term toxicity				
F344 rats and B6C3F$_1$ mice exposed to 0, 0.5, 2, 6 or 15 ppm (0, 0.6, 2.4, 7.2 or 18 mg/m^3) formaldehyde for 6 hours/day for 3 days.	2.4 mg/m^3 (rats) 7.2 mg/m^3 (mice)	7.2 mg/m^3 (rats) 18 mg/m^3 (mice)	Increased cell proliferation in nasal cavity. In rats, a small transient increase in cell proliferation was observed following exposure to 0.6 mg/m^3 (and to a lesser extent to 2.4 mg/m^3) after 1 day of exposure only. [*number and sex of animals not specified*]	Swenberg *et al.*, 1983, 1986
Groups of six male F344 rats exposed to 0, 0.5, 2, 5.9 or 14.4 ppm (0, 0.6, 2.4, 7.1 or 17.3 mg/m^3) formaldehyde for 6 hours/day, 5 days/week, for 1, 2, 4, 9 or 14 days.	2.4 mg/m^3	7.1 mg/m^3	Histopathological effects in nasal cavity. Inhibition of mucociliary clearance.	Morgan *et al.*, 1986b
Groups of 10 male Wistar rats exposed to 0, 5 or 10 ppm (0, 6 or 12 mg/m^3) formaldehyde for 8 hours/day ("continuous exposure") or to 10 or 20 ppm (12 or 24 mg/m^3) formaldehyde for eight 30-minute exposure periods separated by 30-minute intervals ("intermittent exposure"), 5 days/week for 4 weeks.		6 mg/m^3	Histopathological effects and increased cell proliferation in nasal cavity. In animals with the same daily cumulative exposure to formaldehyde, the effects were greater in animals exposed intermittently to the higher concentration.	Wilmer *et al.*, 1987
Groups of three male rhesus monkeys exposed to 0 or 6 ppm (0 or 7.2 mg/m^3) formaldehyde for 6 hours/day, 5 days/week, for either 1 or 6 weeks.		7.2 mg/m^3	Histopathological effects and increased cell proliferation in nasal cavity and upper portions of respiratory tract. [*exposure to formaldehyde had no histopathological effect on the lungs or other internal organs*]	Monticello *et al.*, 1989
Groups of 10 male Wistar rats exposed to 0, 0.3, 1.1 or 3.1 ppm (0, 0.36, 1.3 or 3.7 mg/m^3) formaldehyde for 22 hours/day for 3 consecutive days.	1.3 mg/m^3	3.7 mg/m^3	Histopathological effects and increased cell proliferation in nasal cavity.	Reuzel *et al.*, 1990
Groups of 36 male F344 rats exposed to 0, 0.7, 2, 6.2, 9.9 or 14.8 ppm (0, 0.8, 2.4, 7.4, 11.9 or 17.8 mg/m^3) formaldehyde for 6 hours/day, 5 days/week, for 1, 4 or 9 days or 6 weeks.	2.4 mg/m^3	7.4 mg/m^3	Histopathological effects and increased cell proliferation in nasal cavity. [*exposure to formaldehyde had no histopathological effect on the lungs, trachea or carina*]	Monticello *et al.*, 1991
Groups of 5–6 Wistar rats exposed to 0, 1, 3.2 or 6.4 ppm (0, 1.2, 3.8 or 7.7 mg/m^3) formaldehyde, 6 hours/day for 3 consecutive days.	1.2 mg/m^3	3.8 mg/m^3	Histopathological effects and increased cell proliferation in nasal cavity.	Cassee *et al.*, 1996
Subchronic toxicity				
Groups of 10 male and female Wistar rats exposed to 0, 1, 9.7 or 19.8 ppm (0, 1.2, 11.6 or 23.8 mg/m^3) formaldehyde for 6 hours/day, 5 days/week, for 13 weeks.	1.2 mg/m^3	11.6 mg/m^3	Histopathological effects in nasal cavity. [*exposure of males to 23.8 mg/m^3 produced non-significant increase in incidence of histopathological effects in the larynx. The authors noted minimal focal squamous metaplasia within the respiratory epithelium in a small number (2/10 males, 1/10 females) of animals exposed to 1.2 mg/m^3*]	Woutersen *et al.*, 1987

Table 2 (continued)

Protocol	Results		Critical effect [*comments*]	Reference
	NO(A)EL	LO(A)EL		
Groups of 10 male Wistar rats exposed to 0, 0.1, 1.0 or 9.4 ppm (0, 0.12, 1.2 or 11.3 mg/m^3) formaldehyde for 6 hours/day, 5 days/week, for 13 weeks.	1.2 mg/m^3	11.3 mg/m	Histopathological effects in nasal cavity. [*exposure to formaldehyde had no effect upon hepatic protein or glutathione levels*]	Appelman *et al.*, 1988
Groups of 50 male and female Wistar rats exposed to 0, 0.3, 1 or 3 ppm (0, 0.4, 1.2 or 3.6 mg/m^3) formaldehyde for 6 hours/day, 5 days/week, for 13 weeks.	1.2 mg/m^3	3.6 mg/m^3	Histopathological effects and increased cell proliferation in nasal cavity. [*mostly qualitative description of histopathological changes in the nasal cavity. Evidence presented of some transiently increased cell proliferation at lower concentrations*]	Zwart *et al.*, 1988
Groups of 25 male Wistar rats exposed to 0, 1 or 2 ppm (0, 1.2 or 2.4 mg/m^3) formaldehyde for 8 hours/day (continuous exposure) or to 2 or 4 ppm (2.4 or 4.8 mg/m^3) formaldehyde in eight 30-minute exposure periods separated by 30-minute intervals (intermittent exposure), 5 days/week for 13 weeks.	2.4 mg/m^3	4.8 mg/m^3	Histopathological effects in nasal cavity. In animals with the same cumulative exposure to formaldehyde (i.e., 19.2 mg/m^3-hours per day), the incidence of substance-related histopathological changes in the respiratory epithelium was increased in animals exposed intermittently to the higher concentration. [*these concentrations of formaldehyde had no significant effect upon cell proliferation in the nasal cavity*]	Wilmer *et al.*, 1989
Groups of 10 male F344 rats exposed to 0, 0.7, 2.0, 5.9, 10.5 or 14.5 ppm (0, 0.8, 2.4, 7.1, 12.6 or 17.4 mg/m^3) formaldehyde for 6 hours/day, 5 days/week, for 11 weeks and 4 days.	2.4 mg/m^3	7.1 mg/m^3	Histopathological effects and increased cell proliferation in nasal cavity.	Casanova *et al.*, 1994
Chronic toxicity				
Groups of cynomolgus monkeys (6 male), rats (20 male and female) and hamsters (10 male and female) exposed to 0, 0.2, 1 or 3 ppm (0, 0.24, 1.2 or 3.6 mg/m^3) formaldehyde for 22 hours/day, 7 days/week, for 26 weeks.	1.2 mg/m^3	3.6 mg/m^3	Monkeys and rats (histopathological effects in nasal cavity). Comparable effects observed in both species.	Rusch *et al.*, 1983
Groups of approximately 120 male and female F344 rats and $B6C3F_1$ mice exposed to 0, 2.0, 5.6 or 14.3 ppm (0, 2.4, 6.7 or 17.2 mg/m^3) formaldehyde for 6 hours/day, 5 days/week, for up to 24 months, followed by an observation period of 6 months.	2.4 mg/m^3 (mice)	2.4 mg/m^3 (rats)	Rats and mice (histopathological effects in nasal cavity).	Swenberg *et al.*, 1980; Kerns *et al.*, 1983
Groups of 10 male Wistar rats exposed to 0, 0.1, 1.0 or 9.4 ppm (0, 0.12, 1.2 or 11.3 mg/m^3) formaldehyde for 6 hours/day, 5 days/week, for 52 weeks.	1.2 mg/m^3	11.3 mg/m^3	Histopathological effects in nasal cavity.	Appelman *et al.*, 1988

TABLE 2 (continued)

Protocol	Results		Critical effect [*comments*]	Reference
	NO(A)EL	LO(A)EL		
Chronic toxicity				
Groups of 30 male Wistar rats exposed to 0, 0.1, 1 or 9.8 ppm (0, 0.12, 1.2 or 11.8 mg/m^3) formaldehyde for 6 hours/day, 5 days/week, for 28 months.	1.2 mg/m^3	11.8 mg/m^3	Histopathological effects in nasal cavity.	Woutersen *et al.*, 1989
Groups of 30 Wistar rats exposed to 0, 0.1, 1 or 9.2 ppm (0, 0.12, 1.2 or 11 mg/m^3) formaldehyde for 6 hours/day, 5 days/week, for 3 months and then observed for a further 25-month period.	1.2 mg/m^3	11 mg/m^3	Histopathological effects in nasal cavity. [*relatively short period of exposure to formaldehyde*]	Woutersen *et al.*, 1989
Groups of approximately 90–150 male F344 rats exposed to 0, 0.7, 2, 6, 10 or 15 ppm (0, 0.8, 2.4, 7.2, 12 or 18 mg/m^3) formaldehyde for 6 hours/day, 5 days/week, for up to 24 months.	2.4 mg/m^3	7.2 mg/m^3	Histopathological effects and increased cell proliferation in nasal cavity.	Monticello *et al.*, 1996
Groups of 32 male F344 rats exposed to 0, 0.3, 2.17 or 14.85 ppm (0, 0.4, 2.6 or 17.8 mg/m^3) formaldehyde for 6 hours/day, 5 days/week, for up to 28 months.	0.4 mg/m^3	2.6 mg/m^3	Histopathological effects in nasal cavity. [*incidence summed for all animals examined during interim and terminal sacrifices*]	Kamata *et al.*, 1997

TABLE 3 Summary of non-neoplastic effect levels (oral exposure) for formaldehyde

Protocol	Results		Critical effect [*comments*]	Reference
	NOEL	LO(A)EL		
Short-term toxicity				
Groups of 10 male and female Wistar rats administered drinking water containing amounts of formaldehyde estimated sufficient to provide target intakes of 0, 5, 25 or 125 mg/kg-bw per day for 4 weeks.	25 mg/kg-bw per day	125 mg/kg-bw per day	Histopathological effects in the forestomach and increase in relative kidney weight. [*exposure to formaldehyde had no effect upon the morphology of the liver or kidneys*]	Til *et al.*, 1988
Subchronic toxicity				
Groups of 15 male and female Sprague-Dawley rats administered drinking water containing amounts of formaldehyde estimated sufficient to achieve target doses of 0, 50, 100 or 150 mg/kg-bw per day for 13 weeks.	50 mg/kg-bw per day	100 mg/kg-bw per day	Reduction in weight gain. [*exposure to formaldehyde had no effect on the blood or urine and produced no histopathological changes in internal organs (including the gastrointestinal mucosa); limited number of endpoints examined; target intakes may not have been achieved*]	Johannsen *et al.*, 1986
Groups of four male and female beagle dogs administered diets containing solutions of formaldehyde in amounts estimated sufficient to achieve target doses of 0, 50, 75 or 100 mg/kg-bw per day for 90 days.	75 mg/kg-bw per day	100 mg/kg-bw per day	Reduction in weight gain. [*exposure to formaldehyde had no effect upon hematological or clinical parameters or organ histopathology (including the gastrointestinal mucosa); limited number of endpoints examined; target intakes may not have been achieved*]	Johannsen *et al.*, 1986
Chronic toxicity				
Groups of 70 male and female Wistar rats administered drinking water containing formaldehyde adjusted to achieve target intakes ranging from 0 to 125 mg/kg-bw per day for up to 2 years. [The average concentration of formaldehyde in the drinking water was 0, 20, 260 or 1900 mg/L in the control, low-, mid- and high-dose groups, respectively.]	15 mg/kg-bw per day	82 mg/kg-bw per day	Histopathological effects in the forestomach and glandular stomach. Reduced weight gain. [*exposure to formaldehyde had no effect upon hematological parameters*]	Til *et al.*, 1989
Groups of 20 male and female Wistar rats administered drinking water containing 0, 0.02%, 0.1% or 0.5% (0, 200, 1000 or 5000 mg/L) formaldehyde for 24 months (for approximate intakes of 0, 10, 50 and 300 mg/kg-bw per day, respectively).	10 mg/kg-bw per day	300 mg/kg-bw per day	Reduced weight gain, altered clinical chemistries and histopathological effects in the forestomach and glandular stomach. [*small group sizes*]	Tobe *et al.*, 1989

mucociliary clearance and histopathological changes within the nasal cavity have been observed in rats exposed acutely to formaldehyde at concentrations of ≥2.6 mg/m^3 (Monteiro-Riviere and Popp, 1986; Morgan *et al.*, 1986a; Bhalla *et al.*, 1991).

2.4.3.2 Short-term and subchronic toxicity

2.4.3.2.1 Inhalation

Histopathological effects and an increase in cell proliferation have been observed in the nasal and respiratory tracts of laboratory animals repeatedly exposed by inhalation to formaldehyde for up to 13 weeks. Most short-term and subchronic inhalation toxicity studies have been conducted in rats, with histopathological effects (e.g., hyperplasia, squamous metaplasia, inflammation, erosion, ulceration, disarrangements) and sustained proliferative response in the nasal cavity at concentrations of 3.7 mg/m^3 and above. Effects were generally not observed at 1.2 or 2.4 mg/m^3, although there have been occasional reports of small, transient increases in epithelial cell proliferation at lower concentrations (Swenberg *et al.*, 1983; Zwart *et al.*, 1988). Owing to the reactivity of this substance as well as to differences in breathing patterns between rodents and primates, adverse effects following short-term inhalation exposure of formaldehyde in rodents are generally restricted to the nasal cavity, while in primates effects may be observed deeper within the respiratory tract. The development of histopathological changes and/or increases in epithelial cell proliferation within the nasal cavity of rats appears to be more closely related to the concentration of formaldehyde to which the animals are exposed than to the total dose (i.e., cumulative exposure) (Swenberg *et al.*, 1983, 1986; Wilmer *et al.*, 1987, 1989).

2.4.3.2.2 Oral exposure

Data on toxicological effects arising from the short-term oral exposure of laboratory animals to formaldehyde are limited to one study in which histopathological effects in the forestomach were not observed in Wistar rats receiving 25 mg/kg-bw per day in drinking water over a period of 4 weeks (Til *et al.*, 1988). Information on toxicological effects of the subchronic oral exposure of laboratory animals to formaldehyde is limited to single studies in rats and dogs, in which the target intakes may not have been achieved (Johannsen *et al.*, 1986). Reduction of weight gain in both species was observed at 100 mg/kg-bw per day; No-Observed-Effect Levels (NOELs) were 50 and 75 mg/kg-bw per day, respectively.

2.4.3.3 Chronic toxicity and carcinogenicity

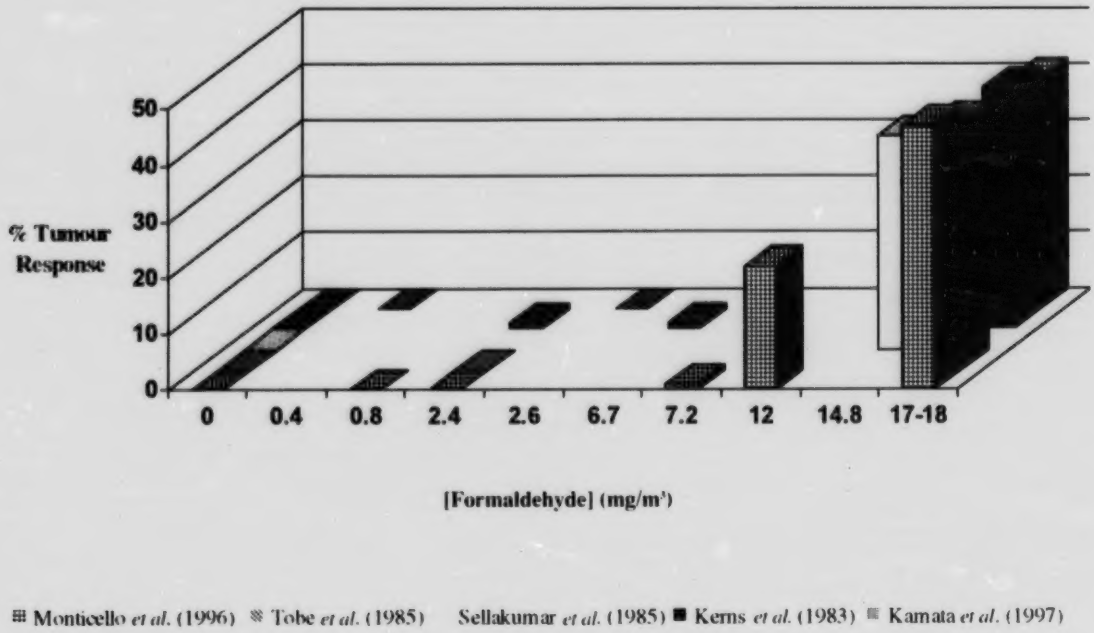
2.4.3.3.1 Chronic toxicity

The principal non-neoplastic effects in animals exposed to formaldehyde by inhalation are histopathological changes (e.g., squamous metaplasia, basal hyperplasia, rhinitis) within the nasal cavity and respiratory tract. Most chronic inhalation toxicity studies have been conducted in rats, with the development of histopathological effects in the nasal cavity being observed at formaldehyde concentrations of 2.4 mg/m^3 and higher (Swenberg *et al.*, 1980; Kerns *et al.*, 1983; Rusch *et al.*, 1983; Appelman *et al.*, 1988; Woutersen *et al.*, 1989; Monticello *et al.*, 1996). The principal non-neoplastic effect in animals exposed orally to formaldehyde is the development of histopathological changes within the forestomach and glandular stomach, with effects in rats at 82 mg/kg-bw per day and above (Til *et al.*, 1989; Tobe *et al.*, 1989).

2.4.3.3.2 Carcinogenicity

An increased incidence of tumours in the nasal cavity was observed in five investigations in which rats were exposed via inhalation to concentrations of formaldehyde greater than 7.2 mg/m^3. Currently, there is no definitive evidence indicating that formaldehyde is carcinogenic when administered orally to laboratory animals. Limited chronic dermal toxicity studies (Krivanek *et al.*, 1983; Iversen, 1988) and older investigations in which animals were injected with formaldehyde (WHO, 1989) add little additional weight to the evidence for the carcinogenicity of formaldehyde in animals.

FIGURE 1 Formaldehyde carcinogenicity



Inhalation

The results of carcinogenesis bioassays by the inhalation route in rats in which there were increases in nasal tumour incidence are presented in Figure 1. Exposure–response in these investigations was similar and highly non-linear, with sharp increases in tumour incidence in the nasal cavity occurring only at concentrations greater than 6 ppm (7.2 mg/m³) formaldehyde. The most extensive bioassay conducted to date in which proliferative responses in the epithelium of various regions of the nasal cavity were investigated is that by Monticello *et al.* (1996).

In a study in which groups of male and female F344 rats were exposed to 0, 2.0, 5.6 or 14.3 ppm (0, 2.4, 6.7 or 17.2 mg/m³) formaldehyde for 6 hours per day, 5 days per week, for up to 24 months, followed by an observation period of 6 months, the incidence of squamous cell carcinoma in the nasal cavity was markedly increased only in the high-concentration groups compared with the unexposed controls. The incidence of this tumour was 0/118, 0/118, 1/119 (1%) and 51/117 (44%) in males and 0/118, 0/118, 1/116 (1%) and 52/119 (44%) in females in the control, low-, mid- and high-concentration groups, respectively (Kerns *et al.*, 1983). Precise histopathological analysis revealed that in animals exposed to the highest concentration of formaldehyde, more than half of the nasal squamous tumours were located on the lateral side of the nasal turbinate and adjacent lateral wall at the front of the nose (Morgan *et al.*, 1986c). Two nasal carcinomas (in male and female rats) and two undifferentiated carcinomas or sarcomas (in male rats) were also observed in animals from the high-concentration groups.

In a follow-up study, Monticello *et al.* (1996) exposed male F344 rats to 0, 0.7, 2, 6, 10 or 15 ppm (0, 0.8, 2.4, 7.2, 12 or 18 mg/m³) formaldehyde for 6 hours per day, 5 days per week, for up to 24 months and assessed tumour incidence within the nasal cavity. Epithelial cell proliferation at seven sites within the nasal cavity (e.g., anterior lateral meatus, posterior lateral meatus, anterior mid-septum, posterior mid-septum, anterior dorsal septum, medial maxilloturbinate and maxillary sinus) was also determined after 3, 6, 12 and 18 months of exposure. The overall incidence of nasal squamous cell carcinoma in animals exposed to 0, 0.8, 2.4, 7.2, 12 or 18 mg/m^3 formaldehyde was 0/90, 0/90, 0/90, 1/90 (1%), 20/90 (22%) and 69/147 (47%), respectively. Tumours were located primarily in the anterior lateral meatus, the posterior lateral meatus as well as the mid-septum.

In a more limited study in which dose–response was not examined, Sellakumar *et al.* (1985) exposed male Sprague-Dawley rats to 0 or 14.8 ppm (0 or 17.8 mg/m^3) formaldehyde for 6 hours per day, 5 days per week, for approximately 2 years. These authors reported a marked increase in the incidence of nasal squamous cell carcinoma — 0/99 and 38/100 in the control and formaldehyde-exposed animals, respectively. These tumours were considered to have arisen primarily from the naso-maxillary turbinates and nasal septum. An increase in the incidence of nasal squamous cell carcinoma was also reported in a study by Tobe *et al.* (1985), in which groups of male F344 rats were exposed to formaldehyde at 0, 0.36, 2.4 or 17 mg/m^3 for 6 hours per day, 5 days per week, for 28 months. Fourteen of 32 animals in the high-concentration group (i.e., 44%) developed nasal squamous cell carcinoma, compared with none in the unexposed (control), low- or mid-concentration groups. In another study in which male F344 rats were exposed to 0, 0.3, 2.17 or 14.85 ppm (0, 0.36, 2.6 or 17.8 mg/m^3) formaldehyde for 6 hours per day, 5 days per week, for up to 28 months, an increased incidence of nasal squamous cell carcinoma was observed in the high-concentration group (Kamata *et al.*, 1997); the overall incidence of nasal tumours among these formaldehyde-exposed animals, dead or sacrificed after 12, 18, 24 and 28 months on study, was 13/32 (41%), compared with 0/32 and 0/32 in two groups of unexposed controls.

Compared with unexposed controls, the incidence of nasal squamous cell carcinoma was not significantly increased in male Wistar rats exposed to formaldehyde at concentrations of 0.12, 1.2 or 11.8 mg/m^3 for 6 hours per day, 5 days per week, for 28 months (i.e., 0% and 4% of the controls and animals exposed to 11.8 mg/m^3, respectively, had nasal cell carcinomas) (Woutersen *et al.*, 1989). However, when animals with noses damaged by electrocoagulation were similarly exposed, the incidence of this tumour type was markedly increased in the high-concentration group (i.e., 1/54, 1/58, 0/56 and 15/58 in animals exposed to 0, 0.12, 1.2 or 11.8 mg/m^3, respectively) (Woutersen *et al.*, 1989).

In other studies in rats, a small but not statistically significant increase in the incidence of tumours of the nasal cavity was observed in animals exposed daily to 20 ppm (24 mg/m^3) formaldehyde for 13 weeks and then observed until 130 weeks (Feron *et al.*, 1988), but not in animals exposed to 9.4 ppm (11.3 mg/m^3) formaldehyde for 52 weeks (Appelman *et al.*, 1988) or to 12.4 ppm (14.9 mg/m^3) formaldehyde for 104 weeks (in either the presence or absence of wood dust at a concentration of 25 mg/m^3) (Holmström *et al.*, 1989a). The lack of observed statistically significant increases in tumour incidence in these investigations may be a function of small group sizes and/or short periods of exposure.

In a study in which groups of male and female B6C3F$_1$ mice were exposed to 0, 2.0, 5.6 or 14.3 ppm (0, 2.4, 6.7 or 17.2 mg/m^3) formaldehyde for 6 hours per day, 5 days per week, for up to 24 months, followed by an observation period of 6 months, there were no statistically significant increases in the incidence of nasal cavity tumours, compared with unexposed controls (Kerns *et al.*, 1983). After 24 months' exposure to formaldehyde, two male mice in the high-concentration group developed squamous cell carcinoma in the nasal cavity. The absence of a significant increase in the incidence of nasal tumours in mice has been attributed, at least in part, to the greater reduction in minute volume in mice than in rats exposed to formaldehyde (Chang *et al.*, 1981; Barrow *et al.*, 1983). The incidence of lung tumours was not increased in an early study in which groups of 42–60 C3H mice (sex not specified) were exposed to formaldehyde at concentrations of 0, 50, 100 or 200 mg/m^3 for three 1-hour periods per week for 35 weeks, although, due to high mortality, treatment in the high-dose group was discontinued in the 4th week, and there was no evaluation of the nasal tissues (Horton *et al.*, 1963). Compared with 132 unexposed controls, there was no increase in the incidence of respiratory tract tumours in 88 male Syrian hamsters exposed to 12 mg formaldehyde/m^3 for their entire lives (Dalbey, 1982).

Oral exposure

In the most comprehensive study identified in male and female Wistar rats administered drinking water containing formaldehyde in amounts estimated to achieve target intakes ranging up to 125 mg/kg-bw per day for up to 2 years, there was no significant increase in tumour incidence compared with unexposed controls (Til *et al.*, 1989). Tobe *et al.* (1989) also reported, although data were not presented, that, compared with unexposed controls, tumour incidence was not increased in small groups of male and female Wistar rats administered drinking water containing up to 5000 mg formaldehyde/L (i.e., providing intakes up to 300 mg/kg-bw per day).

In contrast, increases in tumours of the hematopoietic system were reported by Soffritti *et al.* (1989), based upon the results of a study in which Sprague-Dawley rats were administered drinking water containing formaldehyde at concentrations ranging from 0 to 1500 mg/L for 104 weeks and the animals observed until death (estimated intakes up to approximately 200 mg/kg-bw per day). The proportion of males and females with leukemias (all "hemolymphoreticular neoplasias," e.g., lymphoblastic leukemias and lymphosarcomas, immunoblastic lymphosarcomas and "other" leukemias) increased from 4% and 3%, respectively, in the controls to 22% and 14%, respectively, in the animals receiving drinking water containing 1500 mg formaldehyde/L. Compared with unexposed controls, there was no dose-related increase in the incidence of stomach tumours in animals receiving formaldehyde. Limitations of this study include the "pooling" of tumour types, the lack of statistical analysis and limited examination of non-neoplastic endpoints. Parenthetically, it should be noted that the incidence of hematopoietic tumours (e.g., myeloid leukemia, generalized histiocytic sarcoma) was not increased in Wistar rats receiving up to 109 mg formaldehyde/kg-bw per day in drinking water for up to 2 years (Til *et al.*, 1989).

Using a rodent model for gastric carcinogenesis in which Wistar rats were "initiated" with N-methyl-N'-nitro-N-nitrosoguanidine, Takahashi *et al.* (1986) provided limited evidence for the tumour-promoting activity of formaldehyde following oral exposure.

2.4.3.4 Genotoxicity and related endpoints

A wide variety of endpoints have been assessed in *in vitro* assays of the genotoxicity of formaldehyde (see IARC, 1995, for a review). Generally, the results of these studies have indicated that formaldehyde is genotoxic at high concentrations (i.e., weakly genotoxic) in both bacterial and mammalian cells *in vitro* (inducing both point and large-scale mutations). Formaldehyde induces mutations in *Salmonella typhimurium* and in *Escherichia coli*, with positive results obtained in the presence or absence of metabolic activation systems. Formaldehyde increases the frequency of chromatid/chromosome aberrations, sister chromatid exchange, as well as gene mutations in a variety of rodent and human cell types. Exposure to formaldehyde increased DNA damage (strand breaks) in human fibroblasts and rat tracheal epithelial cells and increased unscheduled DNA synthesis in rat nasoturbinate and maxilloturbinate cells.

Exposure of male Sprague-Dawley rats to 0.5, 3 or 15 ppm (0.6, 3.6 or 18 mg/m^3) formaldehyde for 6 hours per day, 5 days per week, for 1 or 8 weeks had no effect upon the proportion of bone marrow cells with cytogenetic anomalies (e.g., chromatid or chromosome breaks, centric fusions) compared with unexposed controls, although animals in the group exposed to the highest concentration had a modest (1.7- to 1.8-fold), statistically significant (i.e., $p < 0.05$) increase in the proportion of pulmonary macrophage with chromosomal aberrations compared with controls (approximately 7% and 4%, respectively) (Dallas *et al.*, 1992). However, Kitaeva *et al.* (1990) observed a statistically significant increase in the proportion of bone marrow cells with chromosomal aberrations (chromatid or chromosome breaks) from female Wistar rats exposed to low concentrations of formaldehyde for 4 hours per day for 4 months — approximately 0.7%, 2.4% and 4% in animals exposed to 0, 0.5 or 1.5 mg/m^3, respectively. In older studies, exposure of male and female F344 rats to approximately 0.5, 5.9 or 14.8 ppm (0.6, 7.1 or 17.8 mg/m^3) formaldehyde for 6 hours per day for 5 consecutive days had no effect upon the frequency of sister chromatid exchange or chromosomal aberrations and mitotic index in blood lymphocytes (Kligerman *et al.*, 1984). Statistically significant ($p < 0.05$) increases in the proportion of cells with micronuclei and nuclear anomalies (e.g., karyorrhexis, pyknosis, vacuolated bodies) were observed in the stomach, duodenum, ileum and colon within 30 hours of administration (by gavage) of 200 mg formaldehyde/kg-bw to male Sprague-Dawley rats (Migliore *et al.*, 1989). No significant evidence of genotoxicity (e.g., micronuclei, chromosomal aberrations) in bone marrow cells, splenic cells or spermatocytes was reported in earlier studies in which various strains of mice were injected intraperitoneally with formaldehyde (Fontignie-Houbrechts, 1981; Gocke *et al.*, 1981; Natarajan *et al.*, 1983).

The mutational profile for formaldehyde varies among cell types and concentration of formaldehyde to which the cells were exposed and includes both point and large-scale changes. In human lymphoblasts, about half of the mutants at the X-linked hprt locus had deletions of some or all of the hprt gene bands; the other half were assumed to have point mutations (Crosby *et al.*, 1988). In a subsequent study, six of seven formaldehyde-induced mutants with normal restriction fragment patterns had point mutations at AT sites, with four of these six occurring at one specific site (Liber *et al.*, 1989). Crosby *et al.* (1988) also examined the mutational spectra induced by formaldehyde at the gpt gene in *E. coli* (Crosby *et al.*, 1988). A 1-hour exposure to 4 mmol formaldehyde/L induced a spectrum of mutants that included large insertions (41%), large deletions (18%) and point mutations (41%), the majority of which were transversions occurring at GC base pairs. Increasing the concentration of formaldehyde to 40 mmol/L resulted in a much more homogeneous spectrum, with 92% of the mutants being produced by a point mutation, 62% of which were transitions at a single AT base pair. In contrast to these findings, when naked plasmid DNA containing the gpt gene was treated with formaldehyde and shuttled through *E. coli*, most of the mutations were found to be frameshifts.

It is the interaction with the genome at the site of first contact, however, that is of greatest interest with respect to the carcinogenicity of formaldehyde (i.e., in the induction of nasal tumours in rats). Formaldehyde-induced DNA–protein crosslinking (DPX) has been observed in the nasal epithelium of rats (Casanova and Heck, 1987; Heck and Casanova, 1987; Casanova *et al.*, 1989, 1994), as well as in epithelia lining the respiratory tract of monkeys (Casanova *et al.*, 1991) exposed via inhalation. DNA–protein crosslinks are considered a marker of mutagenic potential, since they may initiate DNA replication errors, resulting in mutation. The exposure–response relationship is highly non-linear, with a sharp increase in DPX at concentrations above 4 ppm (4.8 mg/m^3) formaldehyde (see also Table 4) without accumulation on repeated exposure (Casanova *et al.*, 1994). Formaldehyde has also induced the formation of DNA–protein crosslinks in a variety of human and rat cell types (Saladino *et al.*, 1985; Bermudez and Delehanty, 1986; Snyder and van Houten, 1986; Craft *et al.*, 1987; Heck and Casanova, 1987; Cosma *et al.*, 1988; Olin *et al.*, 1996). In 5 of 11 squamous cell carcinomas from rats exposed to 15 ppm (18 mg/m^3) for up to 2 years, there were point mutations at the GC base pairs in the p53 cDNA sequence (Recio *et al.*, 1992).

TABLE 4 Comparative effects of formaldehyde exposure upon cell proliferation, DNA–protein crosslinking and tumour incidence

Formaldehyde concentration, mg/m³ (ppm)	Cell proliferation ([³H]thymidine-labelled cells/mm basement membrane) [1]			DNA–protein crosslink formation (pmol [¹⁴C]formaldehyde bound/mg DNA) [2]		Incidence of nasal carcinoma [3]			
	Anterior lateral meatus	Posterior lateral meatus	Anterior mid-septum	"high tumour region"	"low tumour region"	All sites	Anterior lateral meatus	Posterior lateral meatus	Anterior mid-septum
0 (0)	10.11	7.69	6.58	0	0	0/90	0/90	0/90	0/90
0.8 (0.7)	10.53	7.82	8.04	5	5	0/90	0/90	0/90	0/90
2.4 (2)	9.83	11.24	12.74	8	8	0/96	0/96	0/96	0/96
7.2 (6)	15.68	9.96	4.15	30	10	1/90	1/90	0/90	0/90
12 (10)	76.79	15.29	30.01	–	–	20/90	12/90	2/90	0/90
18 (15)	93.22	59.52	75.71	150	60	69/147	17/147	9/147	8/147

[1] Cell proliferation measured in three locations of the nasal epithelium in male F344 rats exposed to the indicated concentrations of formaldehyde, 6 hours per day, 5 days per week, for 3 months (Monticello *et al.*, 1996).

[2] Extent of DNA–protein crosslink formation measured in two regions of the nasal cavity (respiratory mucosa) in male F344 rats exposed to the indicated concentrations of formaldehyde, 6 hours per day, 5 days per week, for about 12 weeks; the complete lateral meatus was designated the "high tumour region"; the "low tumour region" comprised the medial aspects of naso- and maxilloturbinates, posterior lateral wall, posterior dorsal septum excluding olfactory region, and nasopharyngeal meatuses (Casanova *et al.*, 1994). Data were derived from graphical representations in the reference cited.

[3] Incidence of nasal tumours within the entire nasal cavity or the anterior lateral meatus, posterior lateral meatus or anterior mid-septum in male F344 rats exposed to the indicated concentrations of formaldehyde, 6 hours per day, 5 days per week, for 24 months (Monticello *et al.*, 1996).

2.4.3.5 Reproductive and developmental toxicity

Other than a significant ($p < 0.01$) weight loss in the dams and a 21% reduction in the mean weight of the fetuses from dams in the highest concentration group, the exposure of pregnant Sprague-Dawley rats to 0, 5.2, 9.9, 20 or 39 ppm (0, 6.2, 11.9, 24 or 46.8 mg/m^3) formaldehyde for 6 hours per day from days 6 though 20 of gestation had no effect upon the mean number of live fetuses, resorptions and implantation sites, or fetal losses per litter; although the occurrence of missing sternebra and delayed ossification of the thoracic vertebra was increased in fetuses from the highest exposure group, the increases were neither statistically significant (i.e., $p > 0.05$) nor concentration-dependent (Saillenfait *et al.*, 1989).

Similarly, although weight gain was significantly ($p < 0.05$) reduced in dams exposed to the highest concentration, exposure of pregnant Sprague-Dawley rats to approximately 2, 5 or 10 ppm (2.4, 6 or 12 mg/m^3) formaldehyde for 6 hours per day on days 6 through 15 of gestation had no substance-related effect upon the number of fetuses with major malformations or skeletal anomalies; reduced ossification of the pubic and ischial bones in fetuses from dams exposed to the two highest concentrations of formaldehyde was attributed to larger litter sizes and small fetal weights. Indices of embryotoxicity (e.g., number of corpora lutea, implantation sites, live fetuses, resorptions, etc.) were not affected by exposure to formaldehyde (Martin, 1990).

2.4.3.6 Immunological and neurological effects

Other than a significant ($p < 0.05$) 9% increase in bacterial pulmonary survival in one study of mice exposed to 15 ppm (18 mg/m^3) (Jakab, 1992), as well as a statistically significant ($p < 0.05$ or 0.01) reduction in serum IgM titres in animals administered 40 or 80 mg/kg-bw per day orally, 5 days per week, for 4 weeks (Vargová *et al.*, 1993), adverse effects on either cell- or humoral-mediated immune responses have generally not been observed in rats or mice exposed to formaldehyde (Dean *et al.*, 1984; Adams *et al.*, 1987; Holmstrom *et al.*, 1989b). Endpoints examined in these studies (Dean *et al.*, 1984; Adams *et al.*, 1987; Holmstrom *et al.*, 1989b) included splenic or thymic weights, bone marrow cellularity, the proportion of splenic B- and T-cells, NK-cell activity, lymphocyte proliferation, the number, function or maturation of peritoneal macrophages, host resistance to bacterial or tumour challenge, and B-cell function through induction of (IgG and IgM) antibodies, with exposures ranging from 1 to 15 ppm (1.2 to 18 mg/m^3) formaldehyde.

Results of studies in laboratory animals have indicated that formaldehyde may enhance their sensitization to inhaled allergens. In female Balb/c mice sensitized to ovalbumin, the serum titre of IgE anti-ovalbumin antibodies was increased approximately 3-fold in animals pre-exposed to 2.0 mg formaldehyde/m^3 for 6 hours per day on 10 consecutive days (Tarkowski and Gorski, 1995). Similarly, exposure of female Dunkin-Hartley guinea pigs, sensitized to airborne ovalbumin, to 0.3 mg formaldehyde/m^3 produced a significant ($p < 0.01$) 3-fold increase in bronchial sensitization, as well as a significant ($p < 0.05$) 1.3-fold increase in serum anti-ovalbumin antibodies (Riedel *et al.*, 1996).

2.4.3.7 Toxicokinetics/metabolism and mode of carcinogenesis

Formaldehyde is formed endogenously during the metabolism of amino acids and xenobiotics. *In vivo*, most formaldehyde is probably bound (reversibly) to macromolecules.

Owing to its reactivity with biological macromolecules, most of the formaldehyde that is inhaled is deposited and absorbed in regions of the upper respiratory tract with which the substance comes into first contact (Heck *et al.*, 1983; Swenberg *et al.*, 1983; Patterson *et al.*, 1986). In rodents, which are obligate nose breathers, deposition and absorption occur primarily in the nasal passages, while in oronasal breathers (such as monkeys and humans), they likely occur primarily in the nasal passages and oral cavity but also in the trachea and bronchus.

Species-specific differences in the actual sites of uptake of formaldehyde and associated lesions of the upper respiratory tract are determined by complex interactions among nasal anatomy, ventilation and breathing patterns (e.g., nasal versus oronasal) (Monticello *et al.*, 1991).

Formaldehyde produces intra- and intermolecular crosslinks within proteins and nucleic acids upon absorption at the site of contact (Swenberg *et al.*, 1983). It is also rapidly metabolized to formate by a number of widely distributed cellular enzymes, the most important of which is NAD^+-dependent formaldehyde dehydrogenase. Metabolism by formaldehyde dehydrogenase occurs subsequent to formation of a formaldehyde–glutathione conjugate. Formaldehyde dehydrogenase has been detected in human liver and red blood cells and in a number of tissues (e.g., respiratory and olfactory epithelium, kidney, brain) in the rat.

Due to its deposition principally within the respiratory tract and rapid metabolism, exposure to high atmospheric concentrations of formaldehyde does not result in an increase in blood concentrations in humans (Heck *et al.*, 1985).

In animal species, the half-life of formaldehyde in the circulation ranges from approximately 1 to 1.5 minutes (Rietbrock, 1969; McMartin *et al.*, 1979). Formaldehyde and formate are incorporated into the one-carbon pathways involved with the biosynthesis of proteins and nucleic acids. Owing to the rapid metabolism of formaldehyde, much of this material is eliminated in the expired air (as carbon dioxide) shortly after exposure. Excretion of formate in the urine is the other major route of elimination of formaldehyde (Johansson and Tjälve, 1978; Heck *et al.*, 1983; Billings *et al.*, 1984; Keefer *et al.*, 1987; Upreti *et al.*, 1987; Bhatt *et al.*, 1988).

The mechanisms by which formaldehyde induces tumours in the respiratory tract of rats are not fully understood. Inhibition of mucociliary clearance is observed in rats exposed acutely to concentrations of formaldehyde greater than 2.4 mg/m^3 (Morgan *et al.*, 1986a). There is also evidence that glutathione-mediated detoxification of formaldehyde within nasal tissues becomes saturated in rats at inhalation exposures above 4 ppm (4.8 mg/m^3) (Casanova and Heck, 1987). This correlates with the non-linear increase in DNA–protein crosslink formation at exposures above this level.

A sustained increase in nasal epithelial cell regenerative proliferation resulting from cytotoxicity and mutation, for which DNA–protein crosslinks serve as markers of potential, have been identified as likely, although not sufficient, factors contributing to the induction of nasal tumours in rats induced by formaldehyde. This hypothesis is based primarily on observation of consistent, non-linear dose–response relationships for all three endpoints (DPX, sustained increases in proliferation and tumours) and concordance of incidence of these effects across regions of the nasal passages (see Table 4).

Increased cellular proliferation as a consequence of epithelial cell toxicity is the most significant determinant of neoplastic progression. The effect of formaldehyde exposure on cell proliferation within the respiratory epithelium of rats has been examined in a number of short-term, subchronic and chronic studies (Swenberg *et al.*, 1983; Wilmer *et al.*, 1987, 1989; Zwart *et al.*, 1988; Reuzel *et al.*, 1990; Monticello *et al.*, 1991, 1996; Casanova *et al.*, 1994). A sustained increase in proliferation of nasal epithelial cells has not been observed following the exposure of rats to concentrations of formaldehyde of ≤ 2.4 mg/m^3 (2 ppm) irrespective of the exposure period. In rats exposed to formaldehyde, increased respiratory epithelial cell proliferation in the nasal cavity was more closely related to the concentration to which the animals were exposed than to the total cumulative dose (Swenberg *et al.*, 1983). The relative magnitude of increase in proliferative response is dependent upon the specific site within the nasal cavity and not always directly related to the length of exposure

(Swenberg *et al.*, 1986; Monticello *et al.*, 1991, 1996; Monticello and Morgan, 1994). The extent of the carcinogenic response following exposure to formaldehyde is also dependent upon the size of the target cell population within specific regions of the nasal cavity (Monticello *et al.*, 1996).

Although direct evidence in humans is lacking, increased epithelial cell proliferation (respiratory and olfactory epithelia) and DNA–protein crosslink formation (middle turbinates, lateral wall and septum and nasopharynx) within the upper respiratory tract have been observed in monkeys exposed to formaldehyde by inhalation (Monticello *et al.*, 1989; Casanova *et al.*, 1991). At similar levels of exposure, concentrations of DNA–protein crosslinks were approximately an order of magnitude less in monkeys than in rats. In rats, the cumulative yield of DNA–protein crosslinks was similar after acute and subchronic exposure, suggesting rapid repair (Casanova *et al.*, 1994). Using a model system in which rat trachea populated with human tracheobronchial epithelial cells were xenotransplanted into athymic mice, Ura *et al.* (1989) reported increased human epithelial cell proliferation following *in situ* exposure to formaldehyde.

2.4.4 Humans

2.4.4.1 Case reports and clinical studies

Reports of death following acute inhalation exposure to formaldehyde were not identified. Ulceration and damage along the gastrointestinal tract have been observed in cases where formaldehyde had been ingested (Kochhar *et al.*, 1986; Nishi *et al.*, 1988; WHO, 1989). There are frequent reports on cases of systemic (e.g., anaphylaxis) or more often localized (e.g., contact dermatitis) allergic reactions attributed to the formaldehyde (or formaldehyde-containing resins) present in household and personal care (and dental) products, clothing and textiles, bank note paper, and medical treatments and devices (Maurice *et al.*, 1986; Feinman, 1988; Ebner and Kraft, 1991; Norton, 1991; Flyvholm and Menné, 1992; Fowler *et al.*, 1992; Ross *et al.*, 1992; Vincenzi *et al.*, 1992; Bracamonte *et al.*, 1995; El Sayed *et al.*, 1995; Wantke *et al.*, 1995).

In a number of clinical studies, eye, nose and throat irritation were experienced by volunteers exposed for short periods to levels of formaldehyde ranging from 0.3 to 3.6 mg/m^3 (Andersen and Mølhave, 1983; Sauder *et al.*, 1986, 1987; Schachter *et al.*, 1986; Green *et al.*, 1987, 1989; Witek *et al.*, 1987; Kulle, 1993; Pazdrak *et al.*, 1993). Mucociliary clearance in the anterior portion of the nasal cavity was reduced following exposure of volunteers to 0.3 mg formaldehyde/m^3 (Andersen and Mølhave, 1983). Based upon the results of experimental studies, it appears that in healthy individuals as well as those with asthma, brief exposure (up to 3 hours) to concentrations of formaldehyde up to 3.6 mg/m^3 had no significant clinically detrimental effect upon lung function (Day *et al.*, 1984; Sauder *et al.*, 1986, 1987; Schachter *et al.*, 1986, 1987; Green *et al.*, 1987; Witek *et al.*, 1987; Harving *et al.*, 1990).

2.4.4.2 Epidemiological studies

2.4.4.2.1 Cancer

Possible associations between formaldehyde and cancers of various organs have been examined extensively in epidemiological studies in occupationally exposed populations. Indeed, there have been over 30 cohort and case–control studies of professionals, including pathologists and embalmers, and industrial workers. In addition, several authors have conducted meta-analyses of the available data.

Relevant risk measures from recent case–control and cohort studies are presented in Tables 5 and 6, respectively.

In most epidemiological studies, the potential association between exposure to formaldehyde and cancer of the respiratory tract has been examined. However, in some

TABLE 5 Summary of risk measures from case–control studies

Cancer[1]	Formaldehyde exposure	Risk measure (95% CI)	Reference (comments)
Oropharynx or hypopharynx SEER population based – Washington State	≥10 years occupational exposure occupational exposure score of ≥20	OR = 1.3 (0.7–2.5) OR = 1.5 (0.7–3.0)	Vaughan *et al.*, 1986a (IARC Working Group noted that different proportions of interviews conducted with next-of-kin cases and controls may have affected odds ratios)
Nasopharynx SEER population based– Washington State	exposure score of ≥20	OR = 2.1 (0.6–7.8)	Vaughan *et al.*, 1986a (IARC Working Group noted that different proportions of interviews conducted with next-of-kin cases and controls may have affected odds ratios)
Nasopharynx SEER population based – Washington State	residential exposure of ≥10 years residential exposure of <10 years	OR = 5.5 (1.6–19.4) OR = 2.1 (0.7–6.6)	Vaughan *et al.*, 1986b (IARC Working Group considered living in a mobile home a poor proxy for exposure
Nasal squamous cell carcinoma Hospital based – Netherlands	occupational exposure assessment A occupational exposure assessment B	OR = 3.0 (1.3–6.4)[2] OR = 1.9 (1.0–3.6)[2]	Hayes *et al.*, 1986 (IARC Working Group noted that a greater proportion of cases than controls were dead and variable numbers of next-of-kin were interviewed, 10% of controls but none of cases, by telephone. Noted also that, although different, results for assessments A & B were both positive)
Squamous cell carcinoma of nasal cavity/paranasal sinus Danish Cancer Registry	occupational exposure without exposure to wood dust	OR = 2.0 (0.7–5.9)	Olsen and Asnaes, 1986 (IARC Working Group noted possibly incomplete adjustment for confounding for wood dust for adenocarcinoma; felt that squamous cell carcinoma less likely to be affected, since no clear association with wood dust) (Small number of cases)
Nasopharynx Connecticut Tumour Registry	highest potential exposure category highest potential exposure category and dying at 68+ years of age	OR = 2.3 (0.9–6.0) OR = 4.0 (1.3–12)	Roush *et al.*, 1987
Oral/oropharynx Population based – Turin, Italy	"any" occupational exposure "probable or definite" occupational exposure	OR = 1.6 (0.9–2.8) OR = 1.8 (0.6–5.5)	Merletti *et al.*, 1991 (Small number of cases with "definite" exposure to formaldehyde)
Larynx SEER population based – Washington State	"high" occupational exposure occupational exposure of ≥10 years occupational exposure score of ≥20	OR = 2.0 (0.2–19.5) OR = 1.3 (0.6–3.1) OR = 1.3 (0.5–3.3)	Wortley *et al.*, 1992
Nasal cavity/paranasal sinus (adenocarcinoma) Population based – France	"any" exposure without exposure to wood dust "any" exposure with medium to high exposure to wood dust "no" exposure but medium to high exposure to wood dust	OR = 8.1 (0.9–72.9) OR = 692 (91.9–5210) OR = 130 (14.1–1191)	Luce *et al.*, 1993 (IARC Working Group noted possible residual confounding by exposure to wood dust)

TABLE 5 (continued)

Cancer[1]	Formaldehyde exposure	Risk measure (95% CI)	Reference (comments)
Nasopharynx Hospital based – Philippines	<15 years of exposure >25 years since first exposure <25 years of age at first exposure	OR = 2.7 (1.1–6.6) OR = 2.9 (1.1–7.6) OR = 2.7 (1.1–6.6)	West *et al.*, 1993 (IARC Working Group noted no control for the presence of Epstein-Barr viral antibodies, for which previous strong association with nasopharyngeal cancer was observed)
Lung Nested – cohort of chemical workers – Texas	likely occupational exposure	OR = 0.62 (0.29–1.36)	Bond *et al.*, 1986
Lung	"long–high" occupational exposure/ (cancer controls/population controls)	OR = 1.5 (0.8–2.8)/ OR = 1.0 (0.4–2.4)	Gérin *et al.*, 1989
Lung (adenocarcinoma) Population based – Montréal, Quebec	"long–high" occupational exposure/ (cancer controls/population controls)	OR = 2.3 (0.9–6.0)/ OR = 2.2 (0.7–7.6)	
Respiratory cancer Nested – cohort of Finnish woodworkers	cumulative exposure of ≥3.6 mg/m^3-months, without minimum 10-year induction period	OR = 0.69 (0.21–2.24)[2]	Partanen *et al.*, 1990
	cumulative exposure of ≥3.6 mg/m^3-months, with minimum 10-year induction period exposure to formaldehyde in wood dust	OR = 0.89 (0.26–3.0)[2] OR = 1.19 (0.31–4.56)[2]	(IARC Working Group noted that there were too few cancers at sites other than the lung for meaningful analysis)
Lung Population based – Missouri	potentially exposed non-smokers	OR = 0.9 (0.2–3.3)	Brownson *et al.*, 1993
Lung Nested – cohort of U.S. automotive foundry workers	occupational exposure with latency period of: 0 years 10 years 15 years 20 years	 OR = 1.31 (0.93–1.85) OR = 1.04 (0.71–1.52) OR = 0.98 (0.65–1.47) OR = 0.99 (0.60–1.62)	Andjelkovich *et al.*, 1994
Multiple myeloma Incident cases in follow-up of cancer prevention study in United States	probably exposed	OR = 1.8 (0.6–5.7)	Boffetta *et al.*, 1989
Multiple myeloma Danish Cancer Registry	males with probable occupational exposure females with probable occupational exposure	OR = 1.1 (0.7–1.6) OR = 1.6 (0.4–5.3)	Heineman *et al.*, 1992 Pottern *et al.*, 1992
Non-Hodgkin's lymphoma Iowa State Health Registry	potential "lower intensity" of exposure potential "higher intensity" of exposure	OR = 1.2 (0.9–1.7) OR = 1.3 (0.5–3.8)	Blair *et al.*, 1993
Ocular melanoma Cases diagnosed or treated at UCSF Ocular Oncology Unit	"ever" exposed to formaldehyde	OR = 2.9 (1.2–7.0)	Holly *et al.*, 1996

[1] SEER = Surveillance, Epidemiology and End Results program of the National Cancer Institute; UCSF = University of California at San Francisco.

[2] Data in parentheses represent 90% confidence interval.

TABLE 6 Summary of risk measures from cohort studies

Cancer	Cohort exposed	Risk measure[1]	Reference (comments)
Brain	male anatomists	SMR = 2.7 (1.3–5.0): *10*	Stroup *et al.*, 1986 (Likely exposure to other substances; no quantitative data on exposure)
Leukemia		SMR = 1.5 (0.7–2.7): *10*	
"Other lymphatic tissues"		SMR = 2.0 (0.7–4.4): *6*	
Nasal cavity and sinus		SMR = 0 (0.7–7.2): *0*	
Larynx		SMR = 0.3 (0–2): *1*	
Lung		SMR = 0.3 (0.1–0.5): *12*	
Multiple myeloma	male abrasives production workers	SIR = 4 (0.5–14): *2*	Edling *et al.*, 1987 (Increases based on only two cases each)
Lymphoma		SIR = 2 (0.2–7.2): *2*	
Pancreas		SIR = 1.8 (0.2–6.6): *2*	
Lung		SIR = 0.57 (0.1–2.1): *2*	
Buccal cavity	garment manufacturing workers	SMR = 343 (118–786)[2]: *4*	Stayner *et al.*, 1988
Connective tissue		SMR = 364 (123–825)[2]: *4*	
Trachea, bronchus and lung		SMR = 114 (86–149)[2]: *39*	
Pharynx		SMR = 111 (20–359)[2]: *2*	
Alimentary tract	resin manufacturing workers	SMR = 134 ($p > 0.05$): *11*	Bertazzi *et al.*, 1989 (Small cohort exposed primarily to low concentrations; few deaths during observation period)
Stomach		SMR = 164 ($p > 0.05$): *5*	
Liver		SMR = 244 ($p > 0.05$): *2*	
Lung		SMR = 69: *6*	
Buccal cavity and pharynx	male pathologists	SMR = 0.52 (0.28–0.89): *13*	Matanoski, 1989
Respiratory system		SMR = 0.56 (0.44–0.77): *77*	
Hypopharynx		SMR = 4.7 (0.97–13.4): *3*	
Pancreas		SMR = 1.4 (1.04–1.88): *47*	
Leukemia		SMR = 1.68 (1.14–2.38): *31*	
Buccal cavity and pharynx	male mortuary workers	PMR = 120 (81–171): *30*	Hayes *et al.*, 1990
Nasopharynx		PMR = 216 (59–554): *4*	
Lymphatic and hematopoietic		PMR = 139 (115–167): *115*	
Colon		PMR = 127 (104–153): *111*	
Trachea, bronchus and lung		PMR = 94.9: *308*	
Lung	male chemical workers employed before 1965	SMR = 123 (110–136): *348*	Gardner *et al.*, 1993 (35% of cohort exposed to >2 ppm [2.4 mg/m^3])
Buccal cavity		SMR = 137 (28–141): *3*	
Pharynx		SMR = 147 (59–303): *7*	
Lung	workers exposed to >2.4 mg formaldehyde/m^3 at one specific plant	SMR = 126 (107–147): *165*	
Nasal cavity	male industrial workers	SPIR = 2.3 (1.3–4.0): *13*	Hansen and Olsen, 1995
Nasopharynx		SPIR = 1.3 (0.3–3.2): *4*	
Lung		SPIR = 1.0 (0.9–1.1): *410*	
Larynx		SPIR = 0.9 (0.6–1.2): *32*	
Oral cavity and pharynx		SPIR = 1.1 (0.7–1.7): *23*	

TABLE 6 (continued)

Cancer	Cohort exposed	Risk measure[1]	Reference (comments)
Nasal cavity	male industrial workers exposed above baseline levels	SPIR = 3.0 (1.4–5.7): *9*	
Buccal cavity and pharynx	male automotive foundry workers	SMR = 131 (48–266): *6*	Andjelkovich *et al.*, 1995
Trachea, bronchus and lung		SMR = 120 (89–158): *51*	(25% of cohort exposed to >1.5 ppm [1.8 mg/m^3])
Nasopharynx	white male industrial workers exposed to ≥0.1 ppm formaldehyde	SMR = 2.7 ($p < 0.05$): *6*	Blair *et al.*, 1986 (4% of cohort exposed to ≥2 ppm [2.4 mg/m^3])
Nasopharynx	white male industrial workers with cumulative exposures of:		Blair *et al.*, 1986
	0 ppm-years	SMR = 530: *1*	(4% of cohort exposed to≥2 ppm [2.4 mg/m^3])
	≤0.5 ppm-years	SMR = 271 ($p > 0.05$): *2*	
	0.51–5.5 ppm-years	SMR = 256 ($p > 0.05$): *2*	
	≥5.5 ppm-years	SMR = 433 ($p > 0.05$): *2*	
Nasopharynx	white male industrial workers co-exposed to particulates with cumulative formaldehyde exposures of:		Blair *et al.*, 1987
	0 ppm-years	SMR = 0: *0*	
	<0.5 ppm-years	SMR = 192: *1*	
	0.5–<5.5 ppm-years	SMR = 403: *2*	
	≥5.5 ppm-years	SMR = 746: *2*	
Nasopharynx	white male industrial workers:		Collins *et al.*, 1988
	exposed for <1 year	SMR = 517 ($p \leq 0.05$): *3*	
	exposed for ≥1 year	SMR = 218 ($p > 0.05$): *3*	
	exposed at one plant with particulates	SMR = 1031 ($p \leq 0.01$): *4*	
Nasopharynx	white male workers, hired between 1947 and 1956, employed at one specific plant for:		Marsh *et al.*, 1996
	<1 year	SMR = 768 ($p > 0.05$): *2*	
	≥1 year	SMR = 1049 ($p < 0.05$): *2*	
Lung	white male industrial workers exposed to ≥0.1 ppm formaldehyde	SMR = 111 (96–127): *210*	Blair *et al.*, 1986 (4% of cohort exposed to ≥2 ppm [2.4 mg/m^3])
	white male industrial workers with ≥20 years since first exposure	SMR = 132 ($p \leq 0.05$): *151*	

TABLE 6 (continued)

Cancer	Cohort exposed	Risk measure[1]	Reference (comments)
	white male industrial workers with cumulative exposures of:		
	0 ppm-years	SMR = 68 (37–113): *14*	
	≤0.5 ppm-years	SMR = 122 (98–150): *88*	
	0.51–5.5 ppm-years	SMR = 100 (80–124): *86*	
	>5.5 ppm-years	SMR = 111 (85–143): *62*	
Lung	wage-earning white males in industrial cohort exposed to formaldehyde and other substances	SMR = 1.4 ($p \leq 0.05$): *124*	Blair *et al.*, 1990a
	wage-earning white males in industrial cohort exposed to formaldehyde	SMR = 1.0 ($p > 0.05$): *88*	
Lung	subjects in industrial cohort less than 65 years of age with cumulative exposures of:		Sterling and Weinkam, 1994
	<0.1 ppm-years	RR = 1.0	
	0.1–0.5 ppm-years	RR = 1.47 (1.03–2.12)[2]	
	0.5–2.0 ppm-years	RR = 1.08 (0.67–1.70)[2]	
	>2.0 ppm-years	RR = 1.83 (1.09–3.08)[2]	
	males in industrial cohort less than 65 years of age with cumulative exposures of:		
	<0.1 ppm-years	RR = 1.0	
	0.1–0.5 ppm-years	RR = 1.50 (1.03–2.19)[2]	
	0.5–2.0 ppm-years	RR = 1.18 (0.73–1.90)[2]	
	>2.0 ppm-years	RR = 1.94 (1.13–3.34)[2]	
Lung	white wage-earning males in industrial cohort with >2 ppm-years of cumulative exposure and exposure durations of:		Blair and Stewart, 1994
	<1 year	(no observed deaths)	
	1–<5 years	SMR = 1.1 ($p > 0.05$): *9*	
	5–<10 years	SMR = 2.8 ($p < 0.05$): *17*	
	>10 years	SMR = 1.0 ($p > 0.05$): *10*	
Lung	white male workers employed at one specific plant for:		Marsh *et al.*, 1996
	<1 year	SMR = 134 ($p < 0.05$): *63*	(25% exposed to >0.7 ppm [0.9 mg/m^3])
	≥1 year	SMR = 119 ($p > 0.05$): *50*	
Lung	white males in industrial cohort with cumulative exposures of:		Callas *et al.*, 1996
	0 ppm-years	RR = 1.00	
	0.05–0.5 ppm-years	RR = 1.46 (0.81–2.61)	
	0.51–5.5 ppm-years	RR = 1.27 (0.72–2.26)	
	>5.5 ppm-years	RR = 1.38 (0.77–2.48)	

[1] Unless otherwise noted, values in parentheses are 95% confidence interval or level of statistical significance. Risk measures are presented here in the format reported in the references cited. Values in *italics* are the number of observed deaths or cases, when specified in the reference cited. Abbreviations are as follows: SMR = standardized mortality ratio; SIR = standardized incidence ratio; PMR = proportionate mortality ratio; SPIR = standardized proportionate incidence ratio; RR = relative risk.

[2] Values in parentheses represent 90% confidence interval.

case–control and cohort studies, increased risks of various non-respiratory tract cancers (e.g., multiple myeloma, non-Hodgkin's lymphoma, ocular melanoma, brain, connective tissue, pancreatic, leukemic, lymphoid and hematopoietic, colon) have occasionally been observed. However, such increases have been reported only sporadically, with little consistent pattern. Moreover, results of toxicokinetic and metabolic studies in laboratory animals and humans indicate that most inhaled formaldehyde is deposited within the upper respiratory tract. Available evidence for these tumours at sites other than the respiratory tract does not, therefore, fulfil traditional criteria of causality (e.g., consistency, biological plausibility) for associations observed in epidemiological studies, and the remainder of this section addresses the tumours for which the weight of evidence is greatest — initially nasal and, subsequently, lung.

In case–control studies (Table 5), while sometimes no increase was observed overall (Vaughan *et al*., 1986a), significantly increased risks of nasopharyngeal cancer (up to 5.5-fold) were observed among workers with 10–25 years of exposure or in the highest exposure category in three out of four investigations (Vaughan *et al*., 1986a; Roush *et al*., 1987; West *et al*., 1993), although there were limitations associated with most of these studies, as noted in Table 5. There was no increase in an additional investigation that is also considered to be limited (Olsen and Asnaes, 1986). In three studies in which the association between formaldehyde and nasal squamous cell carcinomas was examined, there were non-significant increases in two (Olsen and Asnaes, 1986; Hayes *et al*., 1990) and no increase in another (Luce *et al*., 1993), although there were limitations (as noted in Table 5) associated with all of these investigations. In the only investigation in which the association between exposure to formaldehyde and adenocarcinoma of the nasal cavity was examined, there was a non-significant increase that was exacerbated in the presence of wood dust (Luce *et al*., 1993), although possible residual confounding by wood dust exposure could not be excluded (Table 5).

There is little convincing evidence of increased risks of nasopharyngeal cancer in cohort studies of populations of professionals or industrial workers occupationally exposed to formaldehyde, although it should be noted that the total number of cases of this rare cancer in all of the studies was small (approximately 15 cases in all studies in Table 6, with some overlap). Risks were not increased in smaller studies of anatomists or mortuary workers (Hayes *et al*., 1990) or in an investigation of proportionate incidence in industrial workers (Hansen and Olsen, 1995); in the latter study, however, the standardized proportionate incidence ratio (SPIR) for cancers of the "nasal cavity" was significantly increased (3-fold) in more exposed workers. In a cohort of 11 000 garment workers, the number of deaths due to cancer of the nasal cavity was considered too small to evaluate (Stayner *et al*., 1988). In a cohort of 14 000 workers employed in six chemical and plastic factories in the United Kingdom for which 35% of the cohort was exposed to >2 ppm (2.4 mg/m^3), only one nasal cancer was observed versus 1.7 expected (Gardner *et al*., 1993). The results of the largest industrial cohort mortality study of 26 561 workers first employed before 1966 at 10 plants in the United States (4% of cohort exposed to ≥2 ppm [2.4 mg/m^3]) indicated an approximately 3-fold excess of deaths due to nasopharyngeal cancer associated with occupational exposure to formaldehyde (Blair *et al*., 1986). However, subsequent analyses revealed that five of the seven observed deaths were among individuals who had also been exposed to particulates; four of the seven observed deaths occurred at one specific industrial plant (Blair *et al*., 1987; Collins *et al*., 1988; Marsh *et al*., 1996). Three of the seven observed deaths due to nasopharyngeal cancer occurred in individuals with less than 1 year of employment (Collins *et al*., 1988), and the four deaths at one specific plant occurred equally in both short-term and long-term workers (Marsh *et al*., 1996).

In most case–control studies, there have been no increases in lung cancer (Bond *et al*., 1986; Gérin *et al*., 1989; Brownson *et al*., 1993; Andjelkovich *et al*., 1994). In the single study where exposure–response was examined, there was no significant increase in adenocarcinoma of the lung for those with "long–high" occupational exposure; although the odds ratio (OR) was greater than for "lung cancer," the number of cases on which this observation was based was small (Gerin *et al.*, 1989). There was no association of relative risks (RR) with latency period (Andjelkovich *et al.*, 1994). In the most extensive investigation of exposure–response, there were no increases in lung cancer in workers subdivided by latency period, although there was a non-significant increase for those co-exposed to wood dust. There was no statistically significant increased risk for "all respiratory cancer" by level, duration, cumulative exposure, duration of repeated exposures to peak levels or duration of exposure to dust-borne formaldehyde, except in one category (Partanen *et al.*, 1990).

In smaller cohort studies of professional and industrial workers (Table 6), there have been no significant excesses of cancers of the trachea, bronchus or lung (Hayes *et al.*, 1990; Andjelkovich *et al.*, 1995), the buccal cavity or pharynx (Matanoski, 1989; Hayes *et al.*, 1990; Andjelkovich *et al.*, 1995), the lung (Stroup *et al.*, 1986; Bertazzi *et al.*, 1989; Hansen and Olsen, 1995) or the respiratory system (Matanoski, 1989). In a cohort of 11 000 garment workers, there was no increase in cancers of the trachea, bronchus or lung, buccal cavity or pharynx (Stayner *et al.*, 1988). In a cohort of 14 000 workers employed in six chemical and plastic factories in the United Kingdom for which 35% of the cohort was exposed to >2 ppm (2.4 mg/m^3), there was a non-significant excess (comparison with local rates) of lung cancers in workers first employed prior to 1965. Among groups employed at individual plants, the standardized mortality ratio (SMR) for lung cancer was significantly increased only in the "highly exposed" subgroup at one plant. However, there was no significant relationship with years of employment or cumulative exposure (Gardner *et al.*, 1993). There was no excess of cancers of the buccal cavity or pharynx in this cohort.

In the largest industrial cohort mortality study of 26 561 workers first employed before 1966 at 10 plants in the United States (4% of cohort exposed to ≥2 ppm [2.4 mg/m^3]), Blair *et al.* (1986) observed a slight but significant (1.3-fold) excess of deaths due to lung cancer among the sub-cohort of white male industrial workers with ≥20 years since first exposure. However, results of a number of follow-up studies within this industrial group have provided little additional evidence of exposure–response (i.e., cumulative, average, peak, duration, intensity) except in the presence of other substances (Blair *et al.*, 1986, 1990a; Marsh *et al.*, 1992, 1996; Blair and Stewart, 1994; Callas *et al.*, 1996).

Meta-analyses of data from epidemiological studies published between 1975 and 1991 were conducted by Blair *et al.* (1990b) and Partanen (1993). These analyses revealed no increased risk of cancer of the oral cavity associated with exposure to formaldehyde (Blair *et al.*, 1990b; Partanen, 1993). Blair *et al.* (1990b) indicated that the cumulative relative risk of nasal cancer was not significantly increased among those with lower (RR = 0.8) or higher (RR = 1.1) exposure to formaldehyde, while Partanen (1993) reported that the cumulative relative risk of sinonasal cancer among those with substantial exposure to formaldehyde was significantly elevated (i.e., RR = 1.75). In both meta-analyses, there was a significantly increased cumulative relative risk (ranging from 2.1 to 2.74) of nasopharyngeal cancer among those in the highest category of exposure to formaldehyde; in the lower or low-medium exposure categories, the cumulative relative risks for nasopharyngeal cancer ranged from 1.10 to 1.59 (Blair *et al.*, 1990b; Partanen, 1993). The analysis of exposure–response in Blair *et al.* (1990b) and Partanen (1993) was based on three and five studies, respectively, in which increased risks of nasopharyngeal cancer had been observed.

Both meta-analyses revealed no increased risk of lung cancer among professionals having exposure to formaldehyde; however, among industrial workers, the cumulative relative risk for lung cancer was marginally (but significantly) increased for those with lower and low-medium (both RR = 1.2) exposure to formaldehyde, compared with those with higher (RR = 1.0) or substantial (RR = 1.1) exposure (Blair *et al.*, 1990b; Partanen, 1993).

More recently, Collins *et al.* (1997) determined the cumulative relative risks of death due to nasal, nasopharyngeal and lung cancer associated with potential exposure to formaldehyde, based upon a meta-analysis of data from case–control and cohort investigations published between 1975 and 1995. For nasal cancer, cumulative relative risks (designated as meta RR) were 0.3 (95% confidence interval [CI] = 0.1–0.9) and 1.8 (95% CI = 1.4–2.3), on the basis of the cohort and case–control studies, respectively. In contrast to the findings of Blair *et al.* (1990b) and Partanen (1993), Collins *et al.* (1997) concluded that there was no evidence of increased risk of nasopharyngeal cancer associated with exposure to formaldehyde; the differing results were attributed to inclusion of additional more recent studies for which results were negative (particularly Gardner *et al.*, 1993) and correction for under-reporting of expected numbers. The authors also considered that the previous analyses of exposure–response were questionable, focusing on only one cohort study and combining the unquantified medium/high-level exposure groups from the case–control studies with the quantified highest exposure group in the one positive cohort study. Although an analysis of exposure–response was not conducted by Collins *et al.* (1997), the authors felt that the case–control data should have been combined with the low-exposure cohort data. Based upon the results of the cohort investigations of industrial workers, pathologists and embalmers, the relative risks for lung cancer were 1.1 (95% CI = 1.0–1.2), 0.5 (95% CI = 0.4–0.6) and 1.0 (95% CI = 0.9–1.1), respectively; the relative risk for lung cancer derived from the case–control studies was 0.8 (95% CI = 0.7–0.9).

2.4.4.2.2 Genotoxicity

An increased incidence of micronucleated buccal or nasal mucosal cells has been reported in some surveys of individuals occupationally exposed to formaldehyde (Ballarin *et al.*, 1992; Suruda *et al.*, 1993; Kitaeva *et al.*, 1996; Titenko-Holland *et al.*, 1996). Evidence of genetic effects (i.e., chromosomal aberrations, sister chromatid exchanges) in peripheral lymphocytes from individuals exposed to formaldehyde vapour has also been reported in some studies (Suskov and Sazonova, 1982; Bauchinger and Schmid, 1985; Yager *et al.*, 1986; Dobiás *et al.*, 1988, 1989; Kitaeva *et al.*, 1996), but not others (Fleig *et al.*, 1982; Thomson *et al.*, 1984; Vasudeva and Anand, 1996; Zhitkovich *et al.*, 1996). Available data are consistent with a pattern of weak positive responses, with good evidence of effects at the site of first contact and equivocal evidence of systemic effects, although the contribution of co-exposures cannot be precluded.

2.4.4.2.3 Respiratory irritancy and function

Symptoms of respiratory irritancy and effects on pulmonary function have been examined in studies of populations exposed to formaldehyde (and other compounds) in both the occupational and general environments.

In a number of studies of relatively small numbers of workers (38–84) in which exposure was monitored for individuals, there was a higher prevalence of symptoms primarily of irritation of the eye and respiratory tract in workers exposed to formaldehyde in the production of resin-embedded fibreglass (Kilburn *et al.*, 1985a), chemicals, and furniture and wood products (Alexandersson and Hedenstierna, 1988, 1989; Holmström and Wilhelmsson, 1988; Malaka and Kodama, 1990) or through employment in the funeral services industry (Holness and Nethercott, 1989), compared with various unexposed control groups. Due to the small numbers of exposed workers, however, it was not possible to meaningfully examine exposure–response in most of these investigations. In the one survey in which it was considered (Horvath *et al.*, 1988), formaldehyde was a statistically significant predictor of symptoms of eye, nose and throat irritation, phlegm, cough and chest complaints. Workers in these studies were exposed to mean formaldehyde concentrations of 0.17 ppm (0.2 mg/m^3) and greater.

Results of investigations of effects on pulmonary function in occupationally exposed populations are somewhat conflicting. Pre-shift reductions (considered indicative of chronic occupational exposure) of up to 12% in parameters of lung function (e.g., forced vital capacity, forced expiratory volume, forced expiratory flow rate) were reported in a number of smaller studies of chemical, furniture and plywood workers (Alexandersson and Hedenstierna, 1988, 1989; Holmström and Wilhelmsson, 1988; Malaka and Kodama, 1990; Herbert *et al.*, 1994). In general, these effects on lung function were small and transient over a workshift, with a cumulative effect over several years that was reversible after relatively short periods without exposure (e.g., 4 weeks); effects were more obvious in non-smokers than in smokers (Alexandersson and Hedenstierna, 1989). In the subset of these investigations in which exposure was monitored for individuals (i.e., excluding only that of Malaka and Kodama, 1990), workers were exposed to mean concentrations of formaldehyde of 0.4 mg/m^3 (0.3 ppm) and greater. In the only study in which it was examined, there was a dose–response relationship between exposure to formaldehyde and decrease in lung function (Alexandersson and Hedenstierna, 1989). However, evidence of diminished lung function was not observed in other studies of larger numbers of workers (84–254) exposed to formaldehyde through employment in wood product (cross-shift decreases that correlated with exposure to formaldehyde but not pre-shift) (Horvath *et al.*, 1988) or resin (Nunn *et al.*, 1990) manufacturing or in the funeral services industry (Holness and Nethercott, 1989). These groups of workers were exposed to mean concentrations of formaldehyde of up to >2 ppm (2.4 mg/m^3).

In a survey of residences in Minnesota, prevalences of nose and throat irritation among residents were low for exposures to concentrations of formaldehyde less than 0.12 mg/m^3 (0.1 ppm) but considerable at levels greater than 0.4 mg/m^3 (0.3 ppm) (Ritchie and Lehnen, 1987). This study involved analysis of the relation between measured levels of formaldehyde and reported symptoms for nearly 2000 residents in 397 mobile and 494 conventional homes. Analyses for formaldehyde in samples collected in two rooms on one occasion were conducted and classified as "low" (<0.1 ppm [0.12 mg/m^3]), "medium" (0.1–0.3 ppm [0.12–0.4 mg/m^3]) and "high" (>0.3 ppm [0.4 mg/m^3]), based on the average value for the two samples. Each of the respondents (who were not aware of the results of the monitoring) was classified by four dependent variables for health effects (yes/no for eye irritation, nose/throat irritation, headaches and skin rash) and four potentially explanatory variables — age, sex, smoking status and low, medium or high exposure to formaldehyde. In all cases, the effects of formaldehyde were substantially greater at concentrations above 0.3 ppm (0.4 mg/m^3) than for levels below 0.3 ppm (0.4 mg/m^3). Reports of eye irritation were most frequent, followed by nose and throat irritation, headaches and skin rash. While proportions of the population reporting eye, nose and throat irritation or headaches at above 0.3 ppm (0.4 mg/m^3) were high (71–99%), those reporting effects at below 0.1 ppm (0.12 mg/m^3) were small (1–2% for eye irritation, 0–11% for nose or throat irritation and 2–10% for headaches). The prevalence of skin rash was between 5% and 44% for >0.3 ppm (0.4 mg/m^3) and between 0% and 3% for <0.1 ppm (0.12 mg/m^3).

There has been preliminary indication of effects on pulmonary function in children in the residential environment associated with relatively low concentrations of formaldehyde, of which further study seems warranted. Although there was no increase in symptoms (chronic cough and phlegm, wheeze, attacks of breathlessness) indicated in self-administered questionnaires, the prevalence of physician-reported chronic bronchitis or asthma in 298 children aged 6–15 years exposed to concentrations between 60 and 140 ppb (72 and 168 µg/m^3) in their homes was increased, especially among those also exposed to ETS (Krzyzanowski *et al.*, 1990). There was an association between exposure and response based on subdivision of the population into groups for which indoor concentrations were ≤40 ppb (48 µg/m^3), 41–60 ppb (48–72 µg/m^3) and >60 ppb (72 µg/m^3), although the proportions of the population in the mid- and highest exposure group were small (<10 and <4%, respectively). Exposure to formaldehyde was characterized based on monitoring in the kitchen, the main living area and each subject's bedroom for two 1-week periods. There was no indication of whether respondents were blinded to the results of the monitoring when responding to the questionnaires. Levels of peak expiratory flow rates (PEFR) also decreased linearly with exposure, with the decrease at 60 ppb (72 µg/m^3) equivalent to 22% of the level of PEFR in non-exposed children; this value was 10% at levels as low as 30 ppb (36 µg/m^3). Effects in a larger sample of 613 adults were less evident, with no increase in symptoms or respiratory disease and small transient decrements in PEFR only in the morning and mainly in smokers, the significance of which is unclear. Results of exposure–response analyses in adults were not presented.

In a survey of 1726 occupants of homes containing UFFI and 720 residents of control homes, health questionnaires were administered and a series of objective tests of pulmonary function, nasal airway resistance, sense of smell and nasal surface cytology conducted (Broder *et al.*, 1988). The distributions of the age groups in this population were 80%, 10% and 10% for 16 and over, <10 and 10–15, respectively; only the questionnaire was completed for children under the age of 10. Monitoring for formaldehyde was conducted in homes of these residents during 2 successive days, one of which included the day on which the occupants were examined, in a central location, in all bedrooms and in the yard. Upon analysis, there were increases in prevalences of symptoms primarily at values greater than 0.12 ppm (0.14 mg/m^3) formaldehyde, although there was evidence of interaction between UFFI and formaldehyde associated with these effects. There were no effects on other parameters investigated, with the exception of a small increase in nasal epithelial squamous metaplasia in UFFI subjects intending to have their UFFI removed. The median concentration of formaldehyde in the UFFI homes was 0.038 ppm (0.046 mg/m^3) (maximum, 0.227 ppm [0.272 mg/m^3]); in the control homes, the comparable value was 0.031 ppm (0.037 mg/m^3) (maximum, 0.112 ppm [0.134 mg/m^3]). Notably, health complaints of residents in UFFI homes were significantly decreased after remediation, although the levels of formaldehyde were unchanged.

2.4.4.2.4 Immunological effects

Epidemiological studies on the effects of exposure to formaldehyde on the immune system have focused primarily upon allergic reactions (reviewed in Feinman, 1988; Bardana and Montanaro, 1991; Stenton and Hendrick, 1994). Case reports of systemic or localized allergic reactions have been attributed to the formaldehyde present in a wide variety of products. Formaldehyde is an irritant to the respiratory tract, and some reports have suggested that the development of bronchial asthma following inhalation of formaldehyde may be due to immunological mechanisms. The specific conditions of exposure as well as idiosyncratic characteristics among individuals are likely important factors in determining whether inhalation exposure to formaldehyde can result in adverse effects on pulmonary function mediated through immunological means. Immune effects (e.g., contact dermatitis) resulting from dermal exposure to formaldehyde have been more clearly defined. The concentration of formaldehyde likely to elicit contact dermatitis reactions in hypersensitive individuals may be as low as 30 ppm. Based on the results of surveys conducted in North America, less than 10% of patients presenting with contact dermatitis may be immunologically hypersensitive to formaldehyde.

2.4.4.2.5 Other effects

Histopathological changes within the nasal epithelium have been examined in surveys of workers occupationally exposed to formaldehyde vapour (Berke, 1987; Edling *et al.*, 1988; Holmström *et al.*, 1989c; Boysen *et al.*, 1990; Ballarin *et al.*, 1992).

In all but one of the most limited of these investigations (Berke, 1987), the prevalence of metaplasia of the nasal epithelium was increased in populations exposed occupationally principally to formaldehyde compared with age-matched control populations; occasionally, also, dysplastic changes were reported in those exposed to formaldehyde. In the most extensive of these investigations and the only one in which there were individual estimates of exposure based on personal and area sampling (Holmström *et al.*, 1989c), mean histological scores were increased in 70 workers principally exposed to formaldehyde (mean 0.3 mg/m^3, standard deviation 0.16 mg/m^3) compared with 36 unexposed controls. Where confounders were examined, they have not explained the effects. For example, in the most extensive study by Holmström *et al.* (1989c), changes were not significant in a population exposed to wood dust–formaldehyde that was also examined. Edling *et al.* (1988) observed no variation in mean histological score in workers exposed to both formaldehyde and wood dust compared with those exposed only to formaldehyde. In cases where it was examined, there was no relationship of histological scores with duration of exposure, although this may be attributable to the small numbers in the subgroups (Edling *et al.*, 1988).

The available data are consistent, therefore, with the hypothesis that formaldehyde is primarily responsible for induction of these histopathological lesions in the nose. The weight of evidence of causality is weak, however, due primarily to the limited number of investigations of relatively small populations of workers that do not permit adequate investigation of, for example, exposure–response.

Based upon recent epidemiological studies, there is no clear evidence to indicate that maternal (Hemminki *et al.*, 1985; John *et al.*, 1994; Taskinen *et al.*, 1994) or paternal (Lindbohm *et al.*, 1991) exposure to formaldehyde is associated with an increased risk of spontaneous abortion.

There is little convincing evidence that formaldehyde is neurotoxic in occupationally exposed populations, although it has been implicated as the responsible agent in the development of neurobehavioural disorders such as insomnia, lack of concentration, memory loss, and mood and balance alterations, as well as loss of appetite in case reports and a series of cross-sectional surveys by the same investigators (Kilburn *et al.*, 1985a,b, 1987, 1989; Kilburn and Warshaw, 1992; Kilburn, 1994). However, the reported effects, which included increases in self-reported symptoms (for which frequencies of behavioural, neurological and dermatological symptoms were sometimes combined for analyses), or impacts on more objective measures of neurobehavioural function were confined primarily to histology workers. Attribution of the effects to formaldehyde in this group is complicated by co-exposures; indeed, sampling and analyses in a small number of histology laboratories confirmed the widely ranging concentrations of formaldehyde, xylene, chloroform and toluene to which such workers were likely exposed. Further, there was no verification of the crude measures by which exposure to formaldehyde was distinguished from that to solvents, which was based on worker recall of time spent conducting various tasks.

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3.0 ASSESSMENT OF "TOXIC" UNDER CEPA 1999

3.1 CEPA 1999 64(a): Environment

The environmental risk assessment of a PSL substance is based on the procedures outlined in Environment Canada (1997a). Analysis of exposure pathways and subsequent identification of sensitive receptors are used to select environmental assessment endpoints (e.g., adverse reproductive effects on sensitive fish species in a community). For each endpoint, a conservative Estimated Exposure Value (EEV) is selected and an Estimated No-Effects Value (ENEV) is determined by dividing a Critical Toxicity Value (CTV) by an application factor. A conservative (or hyperconservative) quotient (EEV/ENEV) is calculated for each of the assessment endpoints in order to determine whether there is potential ecological risk in Canada. If these quotients are less than one, it can be concluded that the substance poses no significant risk to the environment, and the risk assessment is completed. If, however, the quotient is greater than one for a particular assessment endpoint, then the risk assessment for that endpoint proceeds to an analysis where more realistic assumptions are used and the probability and magnitude of effects are considered. This latter approach involves a more thorough consideration of sources of variability and uncertainty in the risk analysis.

3.1.1 Assessment endpoints

Formaldehyde enters the Canadian environment mainly from natural and anthropogenic combustion sources, from industrial on-site releases, from off-gassing of formaldehyde products, and through secondary formation as a result of oxidation of anthropogenic and natural organic compounds in air. Almost all releases and formation in the ambient environment are in air, with small amounts released to water.

Given its physical-chemical properties, formaldehyde is degraded by various processes in air, with very small amounts transferring into water. When released to water or soil, formaldehyde is expected to remain primarily in the original compartment of release, where it undergoes various biological and physical degradation processes. Formaldehyde is not bioaccumulative or persistent in any compartment of the environment.

Based on the sources and fate of formaldehyde in the ambient environment, biota are expected to be exposed to formaldehyde primarily in air and, to a lesser extent, in water. Little exposure of soil or benthic organisms is expected. While formaldehyde occurs naturally in plants and animals, it is readily metabolized and does not bioaccumulate in organisms. Therefore, the focus of the environmental risk characterization will be on terrestrial and aquatic organisms exposed directly to ambient formaldehyde in air and water.

3.1.1.1 Terrestrial

Data on terrestrial toxicity are available for a variety of microorganisms, plants and invertebrates (Section 2.4.1.1), as well as from mammalian toxicology studies (Section 2.4.3). The most sensitive identified endpoints include primarily effects on the growth and development of plants (Haagen-Smit *et al.*, 1952; Barker and Shimabuku, 1992; Mutters *et al.*, 1993).

Bacteria and fungi are ubiquitous in terrestrial ecosystems and, as saprophytes, are essential for nutrient cycling. Terrestrial plants are primary producers, provide food and cover for animals, and provide soil cover to reduce erosion and moisture loss. Invertebrates are an important component of the terrestrial ecosystem, consuming both plant and animal matter while serving as forage for other animals. Vertebrate wildlife are key consumers in most terrestrial ecosystems.

Therefore, although limited, the available toxicity studies cover an array of organisms from different taxa and ecological niches and are considered adequate for an assessment of risks to terrestrial biota. The single most sensitive response for all of these endpoints will be used as the CTV for the risk characterization for terrestrial effects.

3.1.1.2 Aquatic

Aquatic toxicity data are available for a variety of algae, microorganisms, invertebrates, fish and amphibians (Section 2.4.1.2). Identified sensitive endpoints include effects on the development and survival of algae and invertebrates (Bills *et al.*, 1977; Bringmann and Kühn, 1980a; Burridge *et al.*, 1995a,b), inhibition of cell multiplication in protozoa (Bringmann and Kühn, 1980a), immobilization of crustaceans (Bills *et al.*, 1977) and mortality in fish (Reardon and Harrell, 1990).

Algae are primary producers in aquatic systems, forming the base of the aquatic food chain, while zooplankton, including protozoans and crustaceans, are consumed by many species of invertebrates and vertebrates. Fish are consumers in aquatic communities and themselves feed piscivorous fish, birds and mammals.

Therefore, although limited, the available studies cover an array of organisms from different taxa and ecological niches and are considered adequate for an assessment of risks to aquatic biota. The response for all of these endpoints that occurs at lowest concentration is the CTV for the risk characterization for aquatic effects.

3.1.2 Environmental risk characterization

3.1.2.1 Terrestrial organisms

Environmental exposure to formaldehyde in air is expected to be greatest near sites of continuous release or formation of formaldehyde, namely in urban centres and near industrial facilities releasing formaldehyde. Extensive recent data for concentrations in air are available for 27 sites, covering a range of industrial, urban, suburban, rural and remote locations in Canada.

3.1.2.1.1 Hyperconservative analysis

The highest reported concentration of formaldehyde in ambient air in Canada is 27.5 µg/m^3. This value was obtained for a 24-hour urban sample collected in Toronto, Ontario, on August 8, 1995. The mean concentration for six measurements made at this site during a 30-day period encompassing this date (July 14 to August 12, 1995) is 22.15 µg/m^3. This mean concentration will be used as the EEV in the hyperconservative analysis of the chronic exposure scenario for terrestrial organisms. A 1-month mean is selected for the EEV because it corresponds to a longer exposure period relative to the life span of test organisms for which data are available.

For the exposure of terrestrial organisms to formaldehyde in air, the CTV is 18 µg/m^3, based on the corresponding amount in fog (9000 µg/L) that affects the growth and reproduction potential of rapeseed (*Brassica rapa*) exposed 4.5 hours per night, 3 nights per week, for 40 days (Barker and Shimabuku, 1992). This value is the lowest from a moderate data set composed of acute and chronic toxicity studies conducted on at least 18 species of terrestrial plants, microorganisms, invertebrates and mammals exposed to air and/or fog water.

The 40-day intermittent exposure of *Brassica rapa* can be considered as chronic exposure (covering a significant portion of a life stage of the organism). For the hyperconservative analysis, the ENEV for terrestrial organisms is derived by dividing the CTV by a factor of 10. This factor accounts for the uncertainty surrounding the conversion of the effect concentration to a no-effect value, the extrapolation from laboratory to field conditions, and interspecies and intraspecies variations in sensitivity. As a result, the ENEV is 1.8 μg/m^3.

The hyperconservative quotient is calculated by dividing the EEV by the ENEV as follows:

$$\text{Quotient} = \frac{\text{EEV}}{\text{ENEV}}$$

$$= \frac{22.15\ \mu g/m^3}{1.8\ \mu g/m^3}$$

$$= 12.3$$

Since the hyperconservative quotient is more than 1, there is a need to proceed to a more realistic analysis of whether formaldehyde emissions cause adverse effects on terrestrial organisms in Canada.

3.1.2.1.2 Conservative analysis

For a conservative analysis, a more realistic estimate of long-term terrestrial exposure would be the highest of 90th percentile values calculated for each monitored site. A highest 90th percentile value is still representative of high-end concentrations at the site of greatest concern, yet it also excludes unusually high measurements, some of which may have been caused by rare ambient conditions or undetected analytical error. Analysis of the abundant data available shows that only once in the last 10 years were such high air concentrations measured in Canada for as long a period (1 month) as that from which the mean was selected for the hyperconservative EEV. Based on these data, the highest 90th percentile value is 7.48 μg/m^3, calculated from 354 measurements made in Toronto, Ontario, between December 6, 1989 and December 18, 1997. This value will be used as the EEV for the conservative analysis of the exposure scenario for terrestrial organisms. For comparison, the 90th percentile value calculated for all 3842 NAPS measurements available between 1997 and 1998 is 5.50 μg/m^3. The overall mean and median are 2.95 and 2.45 μg/m^3, respectively.

For a conservative analysis, a more realistic ENEV could be calculated by dividing the hyperconservative CTV of 18 μg/m^3 (rapeseed) by a more refined application factor. According to Fletcher *et al*. (1990), there is remarkable agreement between field and laboratory EC_{50} values for plant species. In a study of sensitivity to pesticides in a wide range of plants, only 3 of 20 field EC_{50} values were 2-fold higher than laboratory EC_{50} values, and only 3 of 20 laboratory EC_{50} values were 2-fold higher than field EC_{50} values. Therefore, no application factor may be necessary for laboratory to field extrapolations for plant effects. Furthermore, data indicated that extrapolations among plant species within a genus can be confidently made without uncertainty factors. When extrapolating from one genus to another within a family, an uncertainty factor of 2 captured 80% of the potential variability. Extrapolations across families within an order or across orders within a class should be discouraged, but, if necessary, factors of 15 and 300 should be used for intraorder and intraclass extrapolations, respectively, to capture 80% of the variability (Chapman *et al*., 1998). In the case of the Barker and Shimabuku (1992) study from which the CTV was selected, the four test species consisted of a deciduous tree (aspen), a coniferous tree (slash pine), a grain crop (wheat) and a seed crop (rapeseed), representing diverse growth forms and morphology from four orders and two classes (monocots and dicots). In two of these, there were no adverse effects at test concentrations, while in a third species (slash pine), there was an arguably adverse increase in top growth at the lowest concentration. Other studies indicate that other acute and chronic effects begin to occur only at airborne concentrations clearly higher than for the rapeseed in fog, even in developmental stages (e.g., lily pollen LOEC of 440 µg/m³). The rapeseed seedling therefore appears to be by far the most sensitive of a variety of species tested. Given the diversity of the data set, only a minimal application factor may be required for interspecies extrapolation. Regarding the extrapolation from effect concentration to no-effect concentration, it should be noted that Barker and Shimabuku (1992) used a relatively low threshold of statistical significance ($\alpha = 0.1$), and effects on the rapeseed did not include any of the visual symptoms such as necrosis observed in other liquid- and gas-phase formaldehyde studies. This may therefore allow for a smaller application factor to be used on the CTV for rapeseed. Therefore, keeping a CTV of 18 µg/m³, the application factor of 10 used in the hyperconservative scenario can be reduced to 2 for the conservative assessment. As a result, the ENEV for the conservative analysis of the exposure scenario for terrestrial organisms will be 9 µg/m³.

The conservative quotient is calculated by dividing the EEV by the ENEV as follows:

$$\text{Quotient} = \frac{\text{EEV}}{\text{ENEV}}$$

$$= \frac{7.48\ \mu\text{g/m}^3}{9\ \mu\text{g/m}^3}$$

$$= 0.83$$

Alternatively, for a conservative analysis, it may also be more realistic to use a CTV from a toxicity study involving exposure to formaldehyde in gas phase in air rather than back-calculating from exposure in fog. Reasons to do this include the exploratory nature of the fog study (Barker and Shimabuku, 1992) from which the hyperconservative CTV was selected. The conversion of fog water concentrations to expected air concentrations in the study could not be verified because variables (temperature, vapour pressure, water solubility, Henry's law constant) required for the conversion were not specified in the study. Reported exposure concentrations represented an estimated average based on the observed rate of degradation in the experimental system. Since formaldehyde in the fog water readily undergoes hydration and degradation, it is not certain how its properties may change its toxicity. Analysis of the terrestrial data set available indicates no other reports of studies on effects of fog or effects as sensitive as those in Barker and Shimabuku (1992). In addition, no data were found on concentrations of formaldehyde in fog in Canada or frequency of fog incidence in urban areas to be able to support an assumption that Canadian biota are being exposed to formaldehyde under such conditions as those used in the experiment. Also, the study did not seem to take into consideration potential exposure to gas-phase formaldehyde in between exposures to formaldehyde in fog. A study of chronic exposure to formaldehyde in gas phase in air may be more realistic.

For the conservative analysis of the exposure of terrestrial organisms to formaldehyde in air, the CTV is 78 µg/m³, based on the lowest average concentration in air that caused a slight imbalance in the growth of shoots and roots in the common bean (*Phaseolus vulgaris*) exposed for 7 hours per day, 3 days per week, for 4 weeks in air (day: 25°C, 40% humidity; night: 14°C, 60% humidity) (Mutters *et al*., 1993). This value was selected as the most sensitive endpoint from a moderate data set composed of acute and chronic toxicity studies conducted on at least 18 species of terrestrial plants, microorganisms, invertebrates and mammals exposed to air and/or fog water.

The 28-day intermittent exposure of the bean plant can be considered as chronic exposure (covering a significant portion of a life stage of the organism). Dividing the CTV by a factor of 10 to account for the uncertainty surrounding the conversion of the effect concentration to a no-effect value, the extrapolation from laboratory to field conditions, and interspecies and intraspecies variations in sensitivity, the resulting ENEV is 7.8 µg/m³. This yields the following conservative quotient:

$$\text{Quotient} = \frac{\text{EEV}}{\text{ENEV}}$$

$$= \frac{7.48\ \mu g/m^3}{7.8\ \mu g/m^3}$$

$$= 0.96$$

This quotient is very close to one.

Given the arguments for reducing the application factor of the hyperconservative rapeseed CTV and the even milder effects observed for the common bean plant (Mutters *et al.* [1993] themselves did not conclude any ill effects from formaldehyde), the application factor can be reduced from 10 to 2 for a more realistic ENEV of 39 µg/m^3. This results in a lower conservative quotient:

$$\text{Quotient} = \frac{\text{EEV}}{\text{ENEV}}$$

$$= \frac{7.48\ \mu g/m^3}{39\ \mu g/m^3}$$

$$= 0.19$$

Since all three conservative quotients are less than 1, it is unlikely that formaldehyde in air causes adverse effects on terrestrial organisms in Canada.

In considering a weight-of-evidence approach, other data similarly do not indicate the likelihood of high risks associated with atmospheric exposure. It is uncertain what the potential ecological impacts could be for sensitive effects such as imbalance in growth of roots and shoots. Based on the toxicity data set available, it appears that plants are most sensitive during their early life stages. In Canada, sensitive early life stages of plants usually occur in the spring. Highest air concentrations of formaldehyde have generally been measured in late summer (August) (Environment Canada, 1999a), when atmospheric formaldehyde formation and photochemical smog formation are greatest. It would therefore appear that only the more tolerant adult plants would be exposed to the highest concentrations. In addition, in studies other than those used in the hyperconservative and conservative scenarios above, there has been considerably more tolerance to exposure to formaldehyde (e.g., no injury at concentrations below 840 µg/m^3 for alfalfa; Haagen-Smit *et al.*, 1952), with no effects on plants at concentrations of 44 mg/m^3 (Wolverton *et al.*, 1984).

A summary of the values used in the environmental risk analysis of formaldehyde in the terrestrial environment is presented in Table 7.

TABLE 7 Summary of the environmental risk analysis for terrestrial organisms

Terrestrial organisms	EEV (µg/m^3)	CTV (µg/m^3)	Application factor	ENEV (µg/m^3)	Quotient
Tier 1: Hyperconservative					
Highest urban mean, rapeseed in fog	22.15	18	10	1.8	12.3
Tier 2: Conservative					
Highest 90th percentile, rapeseed in fog	7.48	18	2	9	0.83
Highest 90th percentile, bean plant in air	7.48	78	10	7.8	0.96
Highest 90th percentile, bean plant in air	7.48	78	2	39	0.19

3.1.2.2 Aquatic organisms

Environmental exposure to formaldehyde in water is expected to be greatest near areas of high atmospheric concentrations (where some formaldehyde can partition from air into water) and near spills or effluent outfalls. Measured concentrations are available in Canada for surface waters, effluents and groundwater. For surface water, data are available on limited sampling at four drinking water treatment plants in urban areas of Ontario and Alberta. Measured concentrations in effluent are available for one of the four industrial plants reporting releases of formaldehyde to water. Groundwater data are available for three industrial sites associated with spills or chronic contamination and six cemeteries in Ontario.

3.1.2.2.1 Hyperconservative analysis

A hyperconservative analysis has been conducted for aquatic organisms exposed to concentrations measured in surface water, effluents and groundwater.

The highest concentration of formaldehyde reported in surface water is 9.0 µg/L, obtained for a sample collected from the North Saskatchewan River near a treatment plant in Edmonton, Alberta (Huck *et al.*, 1990). The highest 1-day concentration identified in an industrial effluent was 325 µg/L (Environment Canada, 1999a). In various groundwater samples, the highest concentration of formaldehyde was 690 000 µg/L at an industrial site (Environment Canada, 1997c). These values will be used as the EEVs in the hyperconservative analysis of aquatic organisms in surface water, effluent and groundwater, respectively. The effluent EEV is based on the conservative assumption that organisms could be living at the point of discharge. The groundwater EEV is based on the conservative assumption that the groundwater could recharge directly to surface water at its full concentration.

For exposure of aquatic animals to formaldehyde in water, the CTV is 100 µg/L, based on the concentration that causes 40–50% mortality after 96 hours in day-old zygotes of the marine alga, *Phyllospora comosa* (Burridge *et al.*, 1995a). This value was selected as the most sensitive endpoint from a large data set composed of toxicity studies conducted on at least 36 species of freshwater and marine aquatic algae, microorganisms, invertebrates, fish and amphibians.

The 96-hour exposure for *Phyllospora comosa* zygotes can be considered as chronic exposure (covering a significant portion of the lifetime of the organism). For a hyperconservative analysis, the ENEV is derived by dividing the CTV by a factor of 10. This factor accounts for the uncertainty in the extrapolation from a chronic EC_{50} to a chronic no-effects value, the extrapolation from laboratory to field conditions, and interspecies and intraspecies variations in sensitivity. The resulting ENEV is 10 µg/L.

The hyperconservative quotients are calculated by dividing the EEV by the ENEV as follows:

Surface water analysis

$$\text{Quotient} = \frac{\text{EEV}}{\text{ENEV}}$$

$$= \frac{9.0\ \mu\text{g/L}}{10\ \mu\text{g/L}}$$

$$= 0.9$$

Since the hyperconservative quotient is less than 1, it is unlikely that formaldehyde causes adverse effects on aquatic organisms in ambient surface water in Canada, and more realistic exposure scenarios need not be considered.

Effluent analysis

$$\text{Quotient} = \frac{\text{EEV}}{\text{ENEV}}$$

$$= \frac{325\ \mu g/L}{10\ \mu g/L}$$

$$= 32.5$$

Since the hyperconservative quotient is greater than 1, it is necessary to consider further the likelihood of biota being exposed to such concentrations in surface water near point sources in Canada.

Groundwater analysis

$$\text{Quotient} = \frac{\text{EEV}}{\text{ENEV}}$$

$$= \frac{690\,000\ \mu g/L}{10\ \mu g/L}$$

$$= 69\,000$$

Since the hyperconservative quotient is greater than 1, it is necessary to consider further the likelihood of biota being exposed to such concentrations in Canada.

3.1.2.2.2 Conservative analysis

For a conservative analysis, more realistic estimates of aquatic exposure must be used. In the case of effluent, dilution can be considered. For a conservative analysis, the hyperconservative EEV of 325 µg/L can be divided by a generic and conservative dilution factor of 10 derived for all types of water bodies to estimate ambient concentrations of formaldehyde near outfalls. This results in a conservative effluent EEV of 32.5 µg/L.

In the case of groundwater, the very high concentrations at one contaminated site were related to a recognized historical contamination that has since been contained and remediated (Environment Canada, 1999a). The next highest concentration reported for groundwater was for an industrial site in New Brunswick (maximum of 8200 µg/L). It is highly unlikely that the groundwater at a single sampling station would recharge directly to surface water. A more realistic representation of groundwater quality at the site could be achieved using the median concentration in groundwater at all sampling stations. The median was 100 µg/L for measurements taken at five wells at the contaminated site during 1996–1997. Assuming some degree of dilution similar to that of effluent in receiving water bodies, the median value can also be divided by the generic and conservative dilution factor of 10 to obtain a conservative estimate of possible concentrations in the event of surface recharge. As a result, the conservative EEV for groundwater is 10 µg/L.

For a conservative analysis, an endpoint should be selected that is more appropriate than that for the CTV used in the hyperconservative analysis, which was based on toxicity to a marine alga endemic to Australia. A more meaningful value can be derived by considering toxicity to the seed shrimp, *Cypridopsis* sp., a common freshwater ostracod, yielding a CTV of 360 µg/L, based on the 96-hour EC_{50} (immobility) for this organism (Bills *et al.*, 1977). This value was selected as the most sensitive endpoint from a large data set composed of toxicity studies conducted on at least 34 freshwater species of aquatic algae, microorganisms, invertebrates, fish and amphibians.

For the conservative analysis, the ENEV is derived by dividing the CTV by a factor of 10. This factor accounts for the uncertainty surrounding the extrapolation from the EC_{50} to a chronic no-effects value, the extrapolation from laboratory to field conditions, and interspecies and intraspecies variations in sensitivity. The resulting ENEV is 36 µg/L.

The conservative quotients are calculated by dividing the EEV by the ENEV as follows:

Effluent analysis

$$\text{Quotient} = \frac{\text{EEV}}{\text{ENEV}}$$

$$= \frac{32.5\ \mu\text{g/L}}{36\ \mu\text{g/L}}$$

$$= 0.9$$

Since the conservative quotient is less than 1, it is unlikely that exposure to concentrations in water resulting from effluent discharge are causing adverse effects on populations of aquatic organisms in Canada.

Groundwater analysis

$$\text{Quotient} = \frac{\text{EEV}}{\text{ENEV}}$$

$$= \frac{10\ \mu\text{g/L}}{36\ \mu\text{g/L}}$$

$$= 0.28$$

Since the conservative quotient is less than 1, it is unlikely that concentrations of formaldehyde in groundwater are causing adverse effects on populations of aquatic organisms in Canada.

A summary of the values used in the environmental risk analysis of formaldehyde in the aquatic environment is presented in Table 8.

3.1.2.3 Discussion of uncertainty

There are a number of potential sources of uncertainty in this environmental risk assessment. Regarding effects of formaldehyde on terrestrial and aquatic organisms, uncertainty surrounds the extrapolation from available toxicity data to potential ecosystem effects. While the toxicity data set included studies on organisms from a variety of ecological niches and taxa, there are relatively few good chronic studies available. To account for these uncertainties, application factors were used in the environmental risk analysis to derive ENEVs.

Regarding environmental exposure, there could be concentrations of formaldehyde in Canada that are higher than those identified and used in this assessment.

TABLE 8 Summary of the environmental risk analysis for aquatic organisms

Aquatic organisms	EEV (µg/L)	CTV (µg/L)	Application factor	ENEV (µg/L)	Quotient
Tier 1: Hyperconservative					
Surface water – marine algae	9.0	100	10	10	0.9
Effluent – marine algae	325	100	10	10	32.5
Groundwater – marine algae	690 000	100	10	10	69 000
Tier 2: Conservative					
Effluent – seed shrimp	32.5	360	10	36	0.9
Groundwater – seed shrimp	10	360	10	36	0.28

For exposure in air, the measurements used in this assessment are considered acceptable because they were selected from an extensive set of recent air monitoring data of urban and other sites, including from sites at or near industrial facilities that use and release formaldehyde in Canada. These sites can also be associated with high concentrations of VOCs associated with secondary formation of formaldehyde. Thus, available data on atmospheric concentrations are considered representative of the highest concentrations likely to be encountered in air in Canada.

Only limited data are available for water, although concentrations of formaldehyde are expected to be low because of the limited releases to these media that have been identified and the limited partitioning of formaldehyde to these compartments from air. The available data on concentrations in groundwater include data from industrial sites of the users of formaldehyde. Since data are not available regarding surface recharge of the contaminated groundwater, the assessment very conservatively assumed that recharge occurred at concentrations equivalent to those measured in the groundwater with minimal dilution.

Despite some data gaps regarding the environmental effects and exposure of formaldehyde, the data available at this time are considered adequate for making a conclusion on the environmental risk of formaldehyde in Canada.

3.2 CEPA 1999 64(b): Environment upon which life depends

Formaldehyde does not deplete stratospheric ozone, and its potential for climate change is negligible. The photolysis of formaldehyde leads to the direct formation of radicals that are active in the formation of ground-level ozone (Carter *et al.*, 1995). In addition, formaldehyde is more reactive with hydroxyl radicals (POCP of 105) than compounds such as ethene that are recognized as important in the formation of ground-level ozone (Bunce, 1996). Given its reactivity and concentrations measured in air in Canada, formaldehyde represented approximately 7.8% of the total volatile organic carbon reactivity, ranking it 4th among non-methane hydrocarbons and carbonyl compounds contributing to the formation of ground-level ozone (Dann and Summers, 1997). Formaldehyde is therefore important in the photochemical formation of ground-level ozone.

3.3 CEPA 1999 64(c): Human health

3.3.1 Estimated population exposure

Estimates of the total daily intake of formaldehyde by six age groups of the general population of Canada were developed primarily to determine the relative contributions from various media. These estimates indicate that the daily intake of formaldehyde via inhalation is consistently less than that estimated for the ingestion of foodstuffs. However, it should be noted that critical effects associated with exposure to formaldehyde occur primarily at the site of first contact (i.e., the respiratory tract following inhalation and the gastrointestinal tract following ingestion) and are related to the concentration of formaldehyde in media to which humans are exposed, rather than the total intake of this substance. For this reason, effects of exposure by inhalation and ingestion are addressed separately.

Due primarily to limitations of available data as a basis for characterization of exposure via ingestion, the principal focus of the assessment is airborne exposure. The less representative assessment for ingestion involves comparison of the concentration of formaldehyde in a limited number of food products with a Tolerable Concentration (ingestion).

The general population in Canada is exposed to low concentrations of formaldehyde in outdoor air and to generally higher concentrations in indoor air. A subset of data from the NAPS program was selected to represent the range and

TABLE 9 Concentrations of formaldehyde in outdoor air and residential indoor air in Canada

Medium of exposure	Number of samples	Mid-points of distributions (µg/m^3)		Upper percentiles of distributions of concentrations (µg/m^3)			
		Median	Mean[5]	75th	90th	95th	97.5th
Outdoor air – NAPS data[1]	2818	2.8	3.3	4.1	6.0	7.3	9.1
Outdoor air – reasonable worst-case site[2]	371	2.9	4.0	4.8	7.3	10.4	17.3
Indoor air – five studies[3]	151	29.8	35.9	46.2	64.8	84.6	104.8
Indoor air – lognormal distribution[4]	–	28.7	–	46.1	70.7	91.2	113.8

[1] Data are for selected suburban (n = 4) and urban (n = 4) sites of the NAPS Program (Dann, 1997, 1999) for the period 1990–1998. Concentrations are slightly lower for the subset of suburban sites and slightly higher for the subset of urban sites. Distributions are positively skewed.

[2] One of the four urban sites (i.e., NAPS site 060418 in Toronto) was selected for the reasonable worst-case purpose.

[3] Data were pooled from five studies of concentrations of formaldehyde in residential indoor air. These studies were conducted at various locations in Canada between 1989 and 1995.

[4] The geometric mean and standard deviation of the pooled data (n = 151) from the five Canadian studies were calculated. A lognormal distribution with the same geometric mean and standard deviation was generated and the upper percentiles of this distribution were estimated.

[5] These are the arithmetic mean concentrations. Since formaldehyde was detected in more than 99% of the samples, censoring of the data for limit of detection was not required.

distribution of concentrations to which the general population of Canada is currently assumed to be exposed via inhalation of outdoor air. The selected data are from sites classified as suburban (n = 4) or urban (n = 4) and include all 24-hour concentrations of formaldehyde (n = 2818) measured at these sites between January 1990 and December 1998 (Health Canada, 2000). The distribution of concentrations is positively skewed, with median, arithmetic mean and upper-percentile concentrations as summarized in Table 9. The distribution of concentrations at one of the four urban sites (i.e., in Toronto) was selected as a reasonable worst case. The distribution of concentrations of formaldehyde at this site is also positively skewed, and statistical parameters of this distribution are summarized in Table 9.

Pooled data (n = 151) from five studies in which concentrations of formaldehyde were measured in the indoor air of residences in Canada between 1989 and 1995 were the basis for the range and distribution of concentrations to which the general population of Canada is currently assumed to be exposed via inhalation of residential indoor air (Health Canada, 2000). Sampling duration was 24 hours in two of the studies selected (n = 47 samples). These samples were collected and analyzed by the same methodologies and by the same laboratory as for the NAPS data referred to above. Passive sampling for 7-day periods and different analytical methodology were employed in the remaining three studies (n = 104). The distributions of concentrations of formaldehyde from the 24-hour active and the 7-day passive samples were compared. These distributions were judged to be sufficiently similar to justify pooling the data from the five studies. Median, arithmetic mean and upper-percentile concentrations of the distribution of pooled concentrations are summarized in Table 9.

The distribution of pooled concentrations is positively skewed. When plotted in 10 µg/m^3 bins, there is a good fit to a lognormal distribution characterized by the same geometric mean (i.e., 28.7 µg/m^3) and standard deviation (2.92). Upper percentiles of this lognormal distribution were calculated and are shown for comparison in Table 9. The values of these percentiles are higher for the lognormal distribution than for the more limited data set. This is to be expected, since the lognormal distribution approaches the x-axis asymptotically.

These data are used to estimate the distribution of time-weighted 24-hour concentrations of formaldehyde to which the general population is exposed (Health Canada, 2000). This requires consideration of the proportion of the 24-hour day that is spent indoors versus the time spent outdoors. Recent deterministic (i.e., point) estimates (EHD, 1998) indicate that, in general, all age groups spend a daily average of 21 hours in indoor environments and 3 hours outdoors in Canada. Probabilistic estimates of the proportion of time spent indoors versus outdoors are more desirable, as these would provide an indication of the distributions of these average estimates, but these estimates were not available. Instead, a mean time spent outdoors of 3 hours is assumed based on the point estimates of time spent indoors and outdoors (EHD, 1998). The distribution of the time spent outdoors is arbitrarily assumed to be normal in shape with an arithmetic standard deviation of 2 hours. In the probabilistic simulation, this distribution is truncated at 0 hours and 9 hours. The time spent indoors is calculated as 24 hours minus the time spent outdoors.

Estimates of the distribution of time-weighted 24-hour concentrations of formaldehyde to which the general population is exposed were developed using simple random sampling with Crystal Ball™ Version 4.0 (Decisioneering, Inc., 1996) and simulations of 10 000 trials. Each trial involves random sampling of the distribution of concentrations in outdoor air and multiplying this by a random sample of the time spent outdoors. This results in an estimate of the concentration-time product for formaldehyde (C_O, in µg-hour/m^3) resulting from exposure to outdoor air. The "time spent indoors" is then calculated as 24 hours minus "time spent outdoors." This "time spent indoors" is then multiplied by a random sample from the distribution of concentrations in indoor air and results in an estimate of the concentration-time product for formaldehyde (C_I, in µg-hour/m^3) resulting from exposure to indoor air. The average 24-hour time-weighted concentration of formaldehyde for each trial is then calculated as $(1/24) \times (C_O + C_I)$ for exposure to outdoor and indoor air.

Two simulations were run. In both simulations, the distribution of concentrations of formaldehyde in outdoor air is represented by a frequency histogram of the data from the eight selected NAPS sites (n = 2818 samples). In the first simulation, the distribution of concentrations of formaldehyde in residential indoor air is represented by a frequency histogram of the pooled data from the five selected studies (n = 151 samples). In the second simulation, the distribution of concentrations of formaldehyde in residential indoor air is represented by an assumed lognormal distribution with the same geometric mean (28.7 µg/m^3) and standard deviation (2.92) as for the pooled data. This assumed lognormal distribution is truncated at 150 µg/m^3, the highest concentration measured among the five studies. It is assumed that the general population is exposed to similar distributions of concentrations in the indoor air of public places. Exposure to formaldehyde in the indoor air of workplaces is not addressed specifically; therefore, the general population is assumed to be exposed to similar concentrations of formaldehyde in the indoor air of all workplaces. Estimates of the median, arithmetic mean and upper percentiles of the distributions of 24-hour time-weighted average concentrations of formaldehyde determined from these probabilistic simulations are summarized in Table 10. The two simulations were each run five times. The relative standard deviations of the upper-percentile estimates of time-weighted average concentrations were calculated to determine the stability of these upper-percentile estimates. These relative standard deviations are also summarized in Table 10. Examples of the shapes of the distributions resulting from the two simulations are available in

Table 10 Probabilistic estimates of 24-hour time-weighted average concentrations of formaldehyde in air

	Mid-points of distributions (μg/m^3)		Upper percentiles of distributions of concentrations (μg/m^3) and relative standard deviations (%)			
	Median	Mean[3]	75th	90th	95th	97.5th
Simulation 1[1]	29	36	46 (± 0.5%)	62 (± 1.3%)	80 (± 1.9%)	97 (± 0.7%)
Simulation 2[2]	24	33	45 (± 1.2%)	75 (± 1.2%)	94 (± 1.6%)	109 (± 1.3%)

[1] In simulation 1, the distribution of concentrations of formaldehyde is represented by a frequency histogram of the pooled data from the five selected studies (n = 151 samples).

[2] For simulation 2, a lognormal distribution of concentrations, truncated at 150 μg/m^3, is assumed. This lognormal distribution has the same geometric mean (28.7 μg/m^3) and standard deviation (2.92) as the distribution of concentrations for the pooled data from the five selected studies.

[3] This is the arithmetic mean concentration.

Health Canada (2000). Based on the assumptions underlying these probabilistic simulations, the estimates summarized in Table 10 indicate that one of every two persons would be exposed to 24-hour average concentrations of formaldehyde in air of 24–29 μg/m^3 or greater (i.e., median concentrations). Similarly, 1 in 20 persons (i.e., 95th percentile) would be exposed to 24-hour average concentrations of formaldehyde in air of 80–94 μg/m^3 or greater.

Based on limited data from the United States, concentrations in drinking water may range up to approximately 10 μg/L, in the absence of specific contributions from the formation of formaldehyde by ozonation during water treatment or from leaching of formaldehyde from polyacetal plumbing fixtures. One-half this concentration (i.e., 5 μg/L) was judged to be a reasonable estimate of the average concentration of formaldehyde in Canadian drinking water, in the absence of other data. Concentrations approaching 100 μg/L were observed in a U.S. study assessing the leaching of formaldehyde from domestic polyacetal plumbing fixtures, and this concentration is assumed to be representative of a reasonable worst case.

Similarly, very few data are available with which to estimate the range and distribution of concentrations of formaldehyde in foods to which the general population in Canada is exposed. According to the limited available data, concentrations of formaldehyde in food are highly variable. In the few studies of the formaldehyde content of foods in Canada, the concentrations of formaldehyde were within the range from less than 0.03 to 14 mg/kg (Health Canada, 2000). However, the proportion of formaldehyde in foods that is bioavailable is unknown.

3.3.2 Hazard characterization

Inhalation, the likely principal route of exposure of the general population to formaldehyde, has been the focus of most studies on the effects of this substance in humans and laboratory animals. Available data on effects following ingestion or dermal exposure to formaldehyde are limited. Since formaldehyde is water soluble, highly reactive with biological macromolecules and rapidly metabolized, adverse effects resulting from exposure are observed primarily in those tissues or organs with which formaldehyde first comes into contact (i.e., the respiratory and gastrointestinal tracts following inhalation and ingestion, respectively).

Effects following inhalation that occur primarily at the site of contact are, therefore, the principal focus of this section.

3.3.2.1 Genotoxicity and carcinogenicity

3.3.2.1.1 Genotoxicity

Results of epidemiological studies in occupationally exposed populations are consistent with a pattern of weak positive responses for genotoxicity, with good evidence of an effect at site of contact (e.g., micronucleated buccal or nasal mucosal cells). Evidence for distal (i.e., systemic) effects is equivocal (chromosomal aberrations and sister chromatid exchanges in peripheral lymphocytes). The contribution of co-exposures to observed effects cannot be precluded.

The results of a large number of *in vitro* assays of a variety of endpoints indicate that formaldehyde is weakly genotoxic in both bacterial and mammalian cells. The spectrum of mutation induced by formaldehyde *in vitro* varies among cell types and concentrations to which cells were exposed but includes both point and large-scale changes. The results of *in vivo* studies in animals are similar to those in humans, with effects at site of contact being observed (e.g., modest increase in the proportion of pulmonary macrophages with chromosomal aberrations in rats following inhalation and cytogenetic alterations in the gastrointestinal epithelium of rats following oral exposure). Evidence of distal (systemic) effects is less convincing. Indeed, in the majority of studies of rats exposed to formaldehyde via inhalation, genetic effects within peripheral lymphocytes or bone marrow cells have not been observed.

Formaldehyde also induces the formation of DNA–protein crosslinks in a variety of human and rat cell types *in vitro* and in the epithelium of the nasal cavity of rats and respiratory tract of monkeys following inhalation, which may contribute to the carcinogenicity of the compound in the nasal cavity of rats through replication errors, resulting in mutation.

Overall, formaldehyde is weakly genotoxic, with effects most likely to be observed *in vivo* in cells from tissues or organs with which the aldehyde comes into first contact.

3.3.2.1.2 Carcinogenicity

Inhalation

In epidemiological studies of occupationally exposed populations, there has been little evidence of a causal association between exposure to formaldehyde and lung cancer. Indeed, results of studies in a rather extensive database of cohort and case–control studies do not fulfil traditional criteria of causality in this regard, such as consistency, strength and exposure–response. Increases in mortality or incidence have not been observed consistently, and, where examined, there has consistently been no evidence of exposure–response. The data for nasal and nasopharyngeal cancer are less clear. In case–control studies, there have been increases in cancers of the nasal or nasopharyngeal cavities that fulfil, at least in part, traditional criteria of causality, with tumours having been observed in workers with highest levels or duration of exposure. It should be noted, though, that measures of exposure in these population-based investigations are rather less reliable than those in the larger, most extensive cohort studies of occupationally exposed populations; moreover, methodological limitations complicate interpretation of several of the case–control studies. Excesses of cancers of the nasal or nasopharyngeal cavities have not been observed consistently in cohort studies. Where there have been excesses, there has been little evidence of exposure–response, although the total number of observed tumours was small.

Five carcinogenicity bioassays have provided consistent evidence that formaldehyde is carcinogenic in rats exposed via inhalation (Kerns *et al.*, 1983; Sellakumar *et al.*, 1985; Tobe *et al.*, 1985; Monticello *et al.*, 1996; Kamata *et al.*, 1997). The incidence of nasal tumours was not significantly increased in mice exposed to formaldehyde by inhalation (Kerns *et al.*, 1983). This has been attributed, at least in part, to the greater reduction in minute volume in mice than in rats exposed to formaldehyde (Chang *et al.*, 1981; Barrow *et al.*, 1983), resulting in lower exposures in mice than in rats (Barrow *et al.*, 1983).

Observation of tumours at the site of contact is consistent with toxicokinetic considerations. Formaldehyde is a highly water-soluble, highly reactive gas that is absorbed quickly at the site of contact. It is also rapidly metabolized, such that exposure to even high concentrations of atmospheric formaldehyde does not result in an increase in blood concentrations.

As described in Section 2.4.3.7, the mechanisms by which formaldehyde induces nasal tumours in rats are not fully understood. However, it has been hypothesized that a sustained increase in epithelial cell regenerative proliferation resulting from cytotoxicity is a requisite precursor in the mode of induction of tumours. Mutation, for which the formation of DNA–protein crosslinks serves as a marker of potential, may also contribute to the carcinogenicity of the compound in the nasal cavity of rats. Studies relevant to assessment of the mode of action include a cancer bioassay (Monticello *et al.*, 1996) in which intermediate endpoints (proliferative response in various regions of the nasal epithelium) have been investigated. The relevant database also includes numerous shorter-term studies in which proliferative response and the formation of DNA–protein crosslinks in the nasal epithelium of rats and other species have been examined following exposure via regimens often similar to those in the cancer bioassays (Swenberg *et al.*, 1983; Casanova and Heck, 1987; Heck and Casanova, 1987; Casanova *et al.*, 1989, 1991, 1994; Monticello *et al.*, 1989, 1991). It should be noted, though, that due to the limited data on intermediate endpoints in most of the cancer bioassays, information available as a basis for direct comparison of the incidence of intermediate lesions (i.e., proliferative response as a measure of cytotoxicity and DPX) and tumours is limited to that presented in Table 4.

In all cases where examined, without exception, sustained cytotoxicity and cellular proliferation were observed in the nasal cavities of the same strain of rats exposed in a similar manner in short-term studies to concentrations or doses that induced nasal tumours in the cancer bioassays (Monticello *et al.*, 1991, 1996). However, the converse is not always true. Similarly, tumours have been observed only at concentrations at which increases in DNA–protein crosslinks have been observed in shorter-term studies in the same strain (Casanova and Heck, 1987; Heck and Casanova, 1987; Casanova *et al.*, 1989, 1994).

In addition, where proliferative response (Monticello *et al.*, 1991, 1996) and DPX (Casanova *et al.*, 1994) have been examined in various regions of the nasal passages, sites at which there are increases are similar to those where tumours have been observed. The concentration–response relationships for DPX, cytotoxicity, proliferative response and tumours are highly non-linear, with significant increases in all endpoints being observed at concentrations of 4 ppm (4.8 mg/m^3) and above (Table 4). This correlates well with the concentration at which mucociliary clearance is inhibited and glutathione-mediated metabolism saturated (i.e., 4 ppm [4.8 mg/m^3]). Histological changes, increased epithelial cell proliferation and DPX are all more closely related to the exposure concentration than to the total cumulative intake or dose of formaldehyde (Swenberg *et al.*, 1983; Casanova *et al.*, 1994).

While the respective roles of DPX, mutation and cellular proliferation in the induction of tumours in the rat nose are not fully delineated, the hypothesized mode of carcinogenesis is in keeping with the growing body of evidence supporting the biological plausibility that prolonged regenerative cell proliferation can be a causal mechanism in chemical carcinogenesis. Regenerative cell proliferation following formaldehyde-induced cytotoxicity increases the number of DNA replications and thus increases the probability of a DNA–protein crosslink initiating a DNA replication error, resulting in a mutation. This proposed mode of action is consistent with the observed inhibition of DNA replication in the rat nose at elevated concentrations (Heck and

Casanova, 1994) and point mutations in the p53 tumour suppressor gene in tumours from the noses of rats exposed to formaldehyde (Recio *et al.*, 1992).

The hypothesized mode of induction of formaldehyde-induced tumours that satisfies several criteria for weight of evidence, including consistency, concordance of exposure–response relationships across intermediate endpoints and biological plausibility and coherence of the database, is likely relevant to humans, at least qualitatively. Increased cell proliferation (Monticello *et al.*, 1989) and DNA–protein crosslink formation (Casanova *et al.* 1991) within epithelia of the upper respiratory tract have been observed in monkeys exposed to formaldehyde vapour. Although not sufficient in itself as a basis for inferring causality, direct evidence on histopathological lesions in the nose of humans exposed primarily to formaldehyde in the occupational environment is consistent with a qualitatively similar response of the upper respiratory tract in humans and experimental animals to formaldehyde. Increased human epithelial cell proliferation following *in situ* exposure to formaldehyde has also been observed in a model system in which rat trachea populated with human tracheobronchial epithelial cells were xenotransplanted into athymic mice (Ura *et al.*, 1989).

Because formaldehyde is highly reactive at the site of contact, dosimetry is of critical importance when extrapolating across species that have significantly different anatomical features of the nasal and respiratory passages and patterns of flow of inhaled air. Since humans as well as other primates are oronasal breathers, compared with rats, which are obligate nose breathers, effects associated with the inhalation of formaldehyde are likely to be observed in a wider area deeper within the respiratory tract. Indeed, in rats exposed to moderate levels of formaldehyde, histopathological changes, increased epithelial cell proliferation as well as DNA–protein crosslink formation are restricted to the nasal cavity; in formaldehyde-exposed monkeys (as surrogates for humans), on the other hand, these effects have been observed further along within the upper respiratory tract. While the epidemiological studies taken as a whole do not provide strong evidence for a causal association between formaldehyde exposure and human cancer, the possibility of increased risk of respiratory cancers, particularly those of the upper respiratory tract, cannot be excluded on the basis of available data.

Based primarily upon data derived from laboratory studies, therefore, the inhalation of formaldehyde under conditions that induce cytotoxicity and sustained regenerative proliferation is considered to present a carcinogenic hazard to humans.

Oral exposure

Epidemiological studies of potential carcinogenic hazards associated with the ingestion of formaldehyde were not identified. Currently, there is no definitive evidence to indicate that formaldehyde is carcinogenic when administered orally to laboratory animals. However, consistent with the known reactivity of this substance with biological macromolecules in the tissue or organ of first contact, histopathological and cytogenetic changes within the gastrointestinal tract have been observed in rats administered formaldehyde orally. These observations and additional consideration of the mode of induction of tumours by formaldehyde lead to the conclusion that under certain conditions of exposure, potential carcinogenic hazard associated with the ingestion of formaldehyde cannot be eliminated.

3.3.2.2 Non-neoplastic effects

Sensory irritation of the eyes and respiratory tract by formaldehyde has been observed consistently in clinical studies and epidemiological (primarily cross-sectional) surveys in occupational and residential environments. The pattern of effects is consistent with increases in symptoms being reported at lowest concentrations, with the eye generally being most sensitive.

At concentrations higher than those generally associated with sensory irritation, generally small, reversible effects on lung function have been noted, although evidence of cumulative decrement in pulmonary function is limited.

Results are consistent with the increased prevalence of histological changes in the nasal epithelium in cross-sectional studies of workers being attributable to formaldehyde (Edling *et al.*, 1988; Holmström *et al.*, 1989c; Boysen *et al.*, 1990; Ballarin *et al.*, 1992). The criterion of biological plausibility for weight of evidence of causality is also satisfied by the convincing evidence in monkeys (Rusch *et al.*, 1983) and rodents of histopathological alterations (degenerative changes consistent with cytotoxicity) within the upper respiratory tract. Other than damage to the gastric epithelium observed following the acute ingestion of large amounts of formaldehyde (Kochhar *et al.*, 1986; Nishi *et al.*, 1988; WHO, 1989), studies on potential changes within the gastrointestinal tract in humans following the long-term ingestion of this substance were not identified. However, histological changes within the surface epithelium of the gastrointestinal tract of rats (e.g., erosions and/or ulcers, hyperkeratosis, hyperplasia, gastritis) have been observed following chronic oral exposure to formaldehyde administered in drinking water, at high concentrations (Til *et al.*, 1989; Tobe *et al.*, 1989).

Formaldehyde is not likely to affect reproduction or development at levels of exposure lower than those associated with adverse health effects at the site of contact. Based upon recent epidemiological studies of occupationally exposed individuals, there is no clear evidence indicating that either maternal or paternal inhalation exposure to formaldehyde is associated with an increased risk of spontaneous abortion (Hemminki *et al.*, 1985; Lindbohm *et al.*, 1991; John *et al.*, 1994; Taskinen *et al.*, 1994). In studies of laboratory animals exposed via inhalation (Saillenfait *et al.*, 1989; Martin, 1990) or oral administration (Seidenberg and Becker, 1987: Wickramaratne, 1987), formaldehyde had no effect on reproduction or fetal development, at levels of exposure less than those causing notable adverse health effects at the site of contact.

Based upon the available although limited data, exposure to formaldehyde is unlikely to be associated with suppression of the immune response. Indeed, the dermal hypersensitivity of some individuals to formaldehyde as well as the results of studies in animals indicate heightened immune responses linked to formaldehyde exposure. Information from epidemiological studies on suppression of the immune response associated with exposure to formaldehyde was not identified. Adverse effects on either cell- or humoral-mediated immune responses have not been consistently observed in studies conducted in laboratory animals (Dean *et al.*, 1984; Adams *et al.*, 1987; Holmström *et al.*, 1989b; Jakab, 1992; Vargová *et al.*, 1993). Although suggested in case reports for some individuals, no clear evidence that formaldehyde-induced asthma was attributable to immunological mechanisms has been identified. However, studies with laboratory animals have revealed that formaldehyde may enhance their sensitization to inhaled allergens (Tarkowski and Gorski, 1995; Riedel *et al.*, 1996).

For the general population, dermal exposure to concentrations of formaldehyde in the vicinity of 1–2% (10 000–20 000 ppm) is likely to cause skin irritation; however, in hypersensitive individuals, contact dermatitis can occur following exposure to formaldehyde at concentrations as low as 0.003% (30 ppm). In North America, less than 10% of patients presenting with contact dermatitis may be immunologically hypersensitive to formaldehyde.

3.3.3 Exposure–response analysis

Cancer and non-neoplastic effects are addressed separately here. However, the weight of evidence indicates that formaldehyde is carcinogenic only at concentrations that induce the obligatory precursor lesion of proliferative regenerative response associated with cytotoxicity, although interaction with DNA must also be taken into account. For consistency with other assessments and for ease of presentation, cancer and non-cancer effects are considered separately here, although, based on consideration of mode of action, they are inextricably linked.

Emphasis in the dose–response analyses for cancer presented below is on a biologically motivated case-specific model that incorporates a two-stage clonal growth model. This model is supported by dosimetry calculations from computational fluid dynamics (CFD) modelling of formaldehyde flux in various regions of the nose and a single-path model for the lower respiratory tract. While this model entails simplification of cancer biology, which requires selection of a number of parameters and use of simplifying assumptions, it is considered to offer improvement over default methodology due to incorporation of as many biological data as possible.

There has been no sensitivity analysis conducted to determine which of the model parameters has greatest impact on risk estimates or to identify which parameters are known with the highest degree of certainty. However, output of the model is considered adequate as a basis to ensure that measures taken to prevent sensory irritation[1] in human populations are sufficiently protective with respect to carcinogenic potential.

3.3.3.1 Inhalation

3.3.3.1.1 Carcinogenicity

There is indisputable evidence that formaldehyde is carcinogenic in rats following inhalation, with the carcinogenic response being limited to the site of contact (e.g., the nasal passages of rodents). While the mechanism of action is not well understood, based primarily upon data derived from laboratory studies, regenerative proliferation associated with cytotoxicity appears to be an obligatory intermediate step in the induction of cancer by formaldehyde. Interaction with genetic material, the potential for which is indicated by DPX, likely also contributes, although the probability of mutation resulting from DPX is unknown.

Available data are also consistent with the hypothesis that humans would respond qualitatively similarly to experimental animals in this regard. However, since formaldehyde is highly reactive at the site of contact, dosimetry is of critical importance in predicting interspecies variations in response, as a function of flux to the tissue and regional tissue susceptibility, due to the significantly different anatomical features of the nasal and respiratory passages between experimental animals and humans.

The approach to dose–response modelling emphasized here, therefore, is biologically based, reflecting the non-linearity in concentration–response relationships for formaldehyde-induced nasal cancer and associated intermediate endpoints and incorporating, to the extent possible, mechanistic data and state-of-the-art analyses for species-specific dosimetry. It incorporates regenerative cell proliferation as a required step in the induction of tumours by formaldehyde and a contribution from mutagenicity (not defined specifically by DPX) that has greatest impact at low exposures through modelling of complex functional relationships for cancer due to actions of formaldehyde on mutation, cell replication and exponential clonal expansion. Species variations in dosimetry are taken into account by CFD modelling of formaldehyde flux in various regions of the nose and a single-path model for the lower respiratory tract of humans.

The outcome is compared with that derived based on empirical default methodology for estimation of tumorigenic concentrations in the experimental range for Priority Substances (Health Canada, 1994). However, it is the biologically motivated case-specific model that is considered to provide the most defensible estimates of cancer risk, on the basis that it

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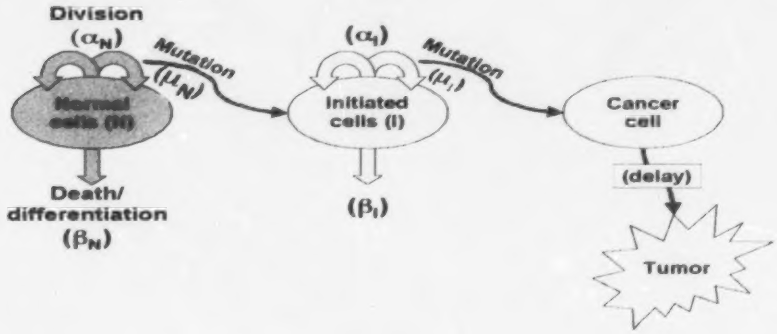
[1] Occurs at lower concentrations than effects on mucociliary clearance or histopathological damage to the nose of humans.

FIGURE 2 Two-stage clonal growth model (reproduced from CIIT, 1999)



encompasses more of the available biological data, thereby offering considerable improvement over default (Health Canada, 1998). Moreover, in view of the clear emphasis herein and preference for the biologically motivated case-specific model, there has been no attempt to incorporate more of the biological data in the calculation of tumorigenic concentrations by default methodology (e.g., dose and time dependence to derive an empirical dose metric for rats).

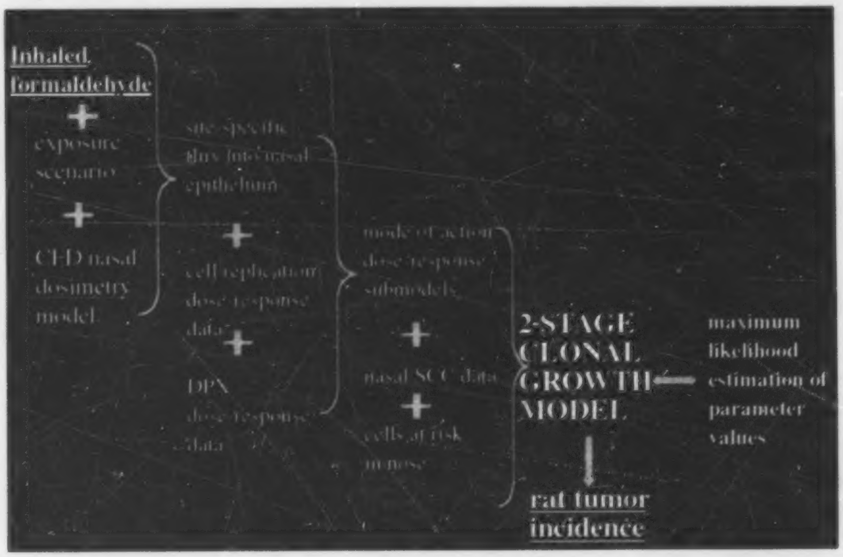
Biologically motivated case-specific model

Derivation of the dose–response model and selection of various parameters are presented in greater detail in CIIT (1999); only a brief summary is provided here. The biologically based, two-stage clonal growth model developed (Figure 2) is identical in biological structure to other such models (also known as MVK models), incorporating information on normal growth, cell cycle time and cells at risk (in various regions of the respiratory tract).

Formaldehyde is assumed to act as a direct mutagen, with the effect considered proportional to the estimated tissue concentration of DNA–protein crosslinks. The dose–response curve for DNA–protein crosslink formation is linear at low exposure concentrations and increases in a greater than linear manner at high concentrations, similar to those administered in the rodent carcinogenicity bioassays. The second mode of carcinogenic action considers cytotoxicity and the subsequent regenerative cellular proliferation associated with exposure to formaldehyde, incorporating a "hockey stick" dose–response curve (i.e., dose threshold curve) within the model. Values for parameters related to the effects of formaldehyde exposure upon the mutagenic (i.e., DNA–protein crosslink formation) and proliferative response (i.e., regenerative cell proliferation resulting from formaldehyde-induced cytotoxicity) were derived from a two-stage clonal growth model developed for rats (Figure 3), which describes the formation of nasal tumours in animals exposed to formaldehyde.

Species-specific dosimetry within various regions of the respiratory tract in laboratory animals and humans was also incorporated. Regional dose is a function of the amount of formaldehyde delivered by inhaled air and the absorption characteristics of the lining within various regions of the respiratory tract. The amount of formaldehyde delivered by inhaled air depends upon major airflow patterns, air-phase diffusion and absorption at the air–lining interface.

FIGURE 3 Roadmap for the rat clonal growth model. SCC = squamous cell carcinoma (reproduced from CIIT, 1999)


Inhaled formaldehyde
+
exposure scenario
+
CFD nasal dosimetry model
site-specific flux into nasal epithelium
+
cell replication dose-response data
+
DPX dose-response data
mode of action dose-response submodels
+
nasal SCC data
+
cells at risk in nose
2-STAGE CLONAL GROWTH MODEL
maximum likelihood estimation of parameter values
rat tumor incidence

The "dose" (flux) of formaldehyde to cells depends upon the amount absorbed at the air–lining interface, mucus/tissue-phase diffusion, chemical interactions such as reactions and solubility, and clearance rates. Species differences in these factors influence the site-specific distribution of lesions.

The F344 rat and rhesus monkey nasal surface for one side of the nose and the nasal surface for both sides of the human nose were mapped at high resolution to develop three-dimensional, anatomically accurate CFD models of rat, primate and human nasal airflow and inhaled gas uptake (Kimbell *et al.*, 1997; Kepler *et al.*, 1998; Subramaniam *et al.*, 1998). The approximate locations of squamous epithelium and the portion of squamous epithelium coated with mucus were mapped onto the reconstructed nasal geometry of the CFD models. These CFD models provide a means for estimating the amount of inhaled gas reaching any site along the nasal passage walls and allow the direct extrapolation of exposures associated with tissue damage from animals to humans via regional nasal uptake. Although development of the biologically based, two-stage clonal growth model for rats required analysis of only the nasal cavity, for humans, carcinogenic risks were based on estimates of formaldehyde dose to regions (i.e., regional flux) along the entire respiratory tract.

The exposure–response model developed for humans (see Figure 4) predicts the additional risk of formaldehyde-induced cancer within the respiratory tract under various exposure scenarios.

Two of the parameters in the human clonal growth model — the probability of mutation per cell division and the growth advantage for preneoplastic cells, both in the absence of formaldehyde exposure, were estimated statistically by fitting the model to human 5-year age group lung cancer incidence data for non-smokers.[2] The parameter representing the time for a malignant cell to expand clonally into a clinically detectable tumour was set at 3.5 years.

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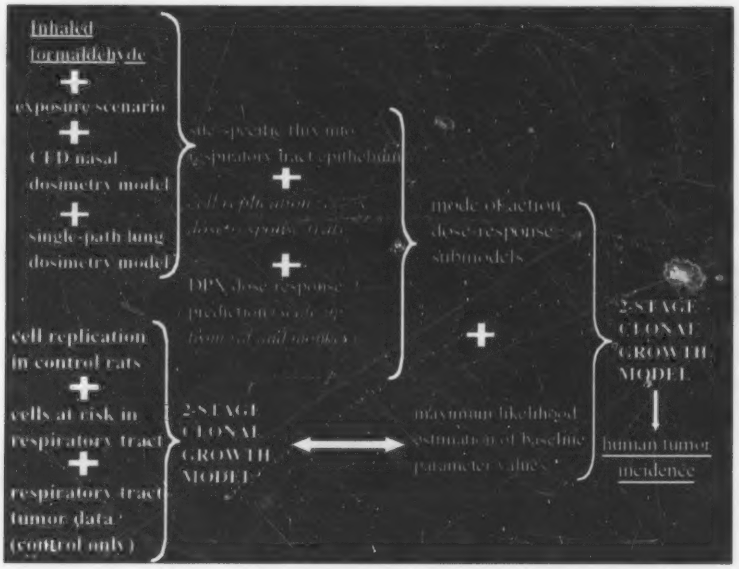
[2] Data on predicted risks of upper respiratory tract cancers for smokers are also presented in CIIT (1999).

FIGURE 4 Roadmap for the human clonal growth model (reproduced from CIIT, 1999)


Inhaled formaldehyde
+
exposure scenario
+
CFD nasal dosimetry model
+
single-path lung dosimetry model
site-specific flux into respiratory tract epithelium
+
cell replication dose-response (rats)
+
DPX dose-response predictions (scale-up from rat and monkey)
mode of action dose-response submodels
+
cell replication in control rats
+
cells at risk in respiratory tract
+
respiratory tract tumor data (control only)
2-STAGE CLONAL GROWTH MODEL
maximum likelihood estimation of baseline parameter values
2-STAGE CLONAL GROWTH MODEL
human tumor incidence

In addition to the human nasal CFD model, a typical-path, one-dimensional model of formaldehyde uptake was developed for the lower respiratory tract. The latter model consisted of the tracheobronchial and pulmonary regions in which uptake was simulated for four ventilatory states, based on an ICRP (1994) activity pattern for a heavy-working adult male. Nasal uptake in the lower respiratory model was calibrated to match overall nasal uptake predicted by the human CFD model. While rodents are obligate nasal breathers, humans switch to oronasal breathing when the level of activity requires a minute ventilation of about 35 L/minute. Thus, two anatomical models for the upper respiratory tract encompassing oral and nasal breathing were developed, each of which consisted basically of a tubular geometry. For the mouth cavity, the choice of tubular geometry was consistent with Fredberg *et al.* (1980). The rationale for using the simple tubular geometry for the nasal airway was based primarily upon the need to remove formaldehyde from the inhaled air at the same rate as in a corresponding three-dimensional CFD simulation. However, in calculations of carcinogenic risk, the nasal airway fluxes predicted by the CFD simulations, and not those predicted by the single-path model, were used to determine upper respiratory tract fluxes.

To account for oronasal breathing, there were two simulations. In one simulation, the nasal airway model represented the proximal upper respiratory tract, while for the other simulation, the mouth cavity model was used for this region. In both simulations, the fractional airflow rate in the mouth cavity or in the nasal airway was taken into account. For each segment distal to the proximal upper respiratory tract, the doses (fluxes) of formaldehyde from both simulations were added to obtain the estimated dose for oronasal breathing. The site-specific deposition of formaldehyde along the human respiratory tract coupled with data on effects upon regional DPX and cell proliferation (derived from studies in animals) (Casanova *et al.*, 1994; Monticello *et al.*, 1996) were reflected in calculations of carcinogenic risks associated with the inhalation of formaldehyde in humans.

Estimates of carcinogenic risks using the human two-stage clonal growth model were developed for typical environmental exposures (i.e., continuous exposure throughout an 80-year lifetime to concentrations of formaldehyde ranging from 0.001 to 0.1 ppm [0.0012 to 0.12 mg/m^3]). The human clonal growth model predicted non-zero additional risks throughout the exposure ranges examined. The two-stage model describes a low-dose, linear carcinogenic response for humans exposed to levels of formaldehyde of ≤0.1 ppm (0.12 mg/m^3), where cytotoxicity and sustained cellular regenerative proliferation do not appear to play a role in tumour induction. Indeed, the effect of formaldehyde upon regenerative cellular proliferation did not have a significant impact upon the predicted carcinogenic risks at exposures between 0.001 and 0.1 ppm (0.0012 and 0.12 mg/m^3). Based upon the two-stage clonal growth model, the predicted additional risks of upper respiratory tract cancer for non-smokers, associated with an 80-year continuous exposure to levels of formaldehyde between 0.001 and 0.1 ppm (1.2 and 120 µg/m^3), range from 2.3×10^{-10} to 2.7×10^{-8}, respectively (CIIT, 1999).

No excess risk was predicted by the human clonal growth model in a cohort exposed to formaldehyde at a specific plant examined in two epidemiological studies (Blair *et al.*, 1986; Marsh *et al.*, 1996). This was consistent with the observed number of cases of respiratory tract cancer (113 observed deaths; 120 expected) in the cohort. Thus, the outcome of the model was consistent with the results of the epidemiological studies.

Default modelling

For comparison, based upon the approach typically employed in the assessment of Priority Substances, a Tumorigenic Concentration$_{05}$ (TC$_{05}$) (i.e., the concentration associated with a 5% increase in tumour incidence over background) of 7.9 ppm (9.5 mg/m^3) (95% lower confidence limit [LCL] = 6.6 ppm [7.9 mg/m^3]) formaldehyde was derived from data on the incidence of nasal squamous tumours in rats exposed to this substance in the single study (i.e., Monticello *et al.*, 1996) in which exposure–response was best characterized.[3] The TC$_{05}$ is calculated by first fitting a multistage model to the exposure–response data. The multistage model is given by

$$P(d) = 1 - e^{-q_0 - q_1 d - \ldots - q_k d^k}$$

where d is dose, k is the number of dose groups in the study minus one, $P(d)$ is the probability of the animal developing a tumour at dose d and $q_i > 0$, $i = 1, \ldots, k$ are parameters to be estimated.

The model was fit using GLOBAL82 (Howe and Crump, 1982), and the TC$_{05}$ was calculated as the concentration C that satisfies

$$\frac{P(C) - P(0)}{1 - P(0)} = 0.05$$

A chi-square lack of fit test was performed for each of the three model fits. The degrees of freedom for this test are equal to k minus the number of q_i's whose estimates are non-zero. A p-value less than 0.05 indicates a significant lack of fit. In this case, chi-square = 3.7, df = 4 and p = 0.45.

3.3.3.1.2 Non-neoplastic effects

There are considered to be sufficient data from clinical studies and cross-sectional surveys of human populations, as well as supporting observations from experimental studies conducted with laboratory animals, to indicate that the irritant effects of formaldehyde on the eyes, nose and throat occur at lowest concentration. Although individual sensitivity and exposure conditions such as temperature, humidity, duration and co-exposure to other irritants are likely to influence response levels, in well-conducted studies, only a very small proportion of the population experiences symptoms of irritation following exposure to ≤0.1 ppm (0.12 mg/m^3) formaldehyde. This is less than the levels that induce mucociliary clearance in the anterior portion of the nasal cavity in available clinical studies in human volunteers (0.3 mg/m^3) and histopathological effects in the nasal epithelium in cross-sectional studies of formaldehyde-exposed workers (0.3 mg/m^3). Additional investigation of preliminary indication of effects on pulmonary function in children in the residential environment associated with lower concentrations of formaldehyde (40–60 ppb [48–72 µg/m^3]) (Krzyzanowski *et al.*, 1990) is warranted.

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[3] Based upon the incidence of nasal tumours in rats exposed to formaldehyde, combined from the studies conducted by Kerns *et al.* (1983) and Monticello *et al.* (1996), the concentration of formaldehyde associated with a 5% increase in tumour incidence (maximum likelihood estimate) was approximately 6.1 ppm (7.3 mg/m^3) (CIIT, 1999).

3.3.3.2 Oral exposure

Lack of evidence for the potential carcinogenicity of ingested formaldehyde precludes an analysis of exposure–response for this effect.

Data on non-neoplastic effects associated with the ingestion of formaldehyde are much more limited than for inhalation. Owing to its high reactivity, non-neoplastic effects in the tissue of first contact following ingestion (i.e., the gastrointestinal tract) are more likely related to the concentration of the formaldehyde consumed, rather than to its cumulative (total) intake. Information from studies on humans is inadequate to identify putative exposure–response relationships with respect to toxicological effects associated with the long-term ingestion of formaldehyde. However, a Tolerable Concentration (TC) for formaldehyde in ingested products may be derived on the basis of the NOEL for the development of histological changes in the gastrointestinal tract of rats as follows:

$$\text{TC} = \frac{260\text{ mg/L}}{100}$$

$$= 2.6\text{ mg/L}$$

where:

- 260 mg/L is the NOEL for effects (i.e., histopathological changes) in the gastrointestinal tract of rats administered formaldehyde in drinking water for 2 years in the most comprehensive study conducted (Til *et al.*, 1989), and
- 100 is the uncertainty factor (×10 for interspecies variation, ×10 for intraspecies variation).

3.3.4 Human health risk characterization

Characterization of human health risks associated with exposure to formaldehyde is based upon analysis of the concentrations of this substance in air and some food products, rather than estimates of total daily intake *per se*, since effects are observed primarily in the tissue of first contact and are related to the level of exposure rather than to total systemic intake.

Emphasis for the characterization of health risks associated with the inhalation of formaldehyde in the environment in Canada is on non-neoplastic effects that occur at lowest concentrations (i.e., sensory irritation). The adequacy of this approach to protect for potential carcinogenicity is considered in the context of the biologically motivated case-specific model described above.

In humans (as well as laboratory animals), signs of ocular and upper respiratory tract sensory irritation have been observed at exposures typically greater than 0.1 ppm [120 µg/m^3]). The estimated median and mean 24-hour time-weighted average exposures to formaldehyde in air in Canada are, at most, one-third of this value. This value is also greater than the estimated time-weighted average exposure to which 95% of the population is exposed. In some indoor locations, however, concentrations may approach the level associated with signs of eye and respiratory tract sensory irritation in humans.

The risks of upper respiratory tract cancer predicted by the biologically motivated case-specific model to be associated with exposure to the median, mean and 95th percentile concentrations of formaldehyde in air in Canada are also exceedingly low (i.e., $<2.7 \times 10^{-8}$). Based on this estimate of risk, priority for investigation of options to reduce exposure in relation to the carcinogenicity of formaldehyde is low.

Available information is considered insufficient to fully characterize the exposure of individuals in Canada to formaldehyde in foodstuffs. However, based upon limited information, the levels of formaldehyde in drinking water appear to be more than 2 orders of magnitude less than the Tolerable Concentration (2.6 mg/L). Although the concentration of formaldehyde in some food products would appear to exceed the Tolerable Concentration, the extent of its bioavailability therein is unknown.

3.3.5 Uncertainties and degree of confidence in human health risk characterization

There is a moderate degree of confidence in the characterization of the principal source of exposure of the general population (i.e., residential indoor air). In the two studies where there was active sampling for a 24-hour duration, the analytical and sampling methodologies were optimum, all of the samples were analyzed by a single specialized laboratory, and the effects of diurnal variation were minimized by the 24-hour sampling duration. The data are also reasonably current (i.e., 1991–1993) and the measured values consistent with those determined in surveys in other countries. While some uncertainty is introduced by pooling of these data with those from the remaining three studies, which involved passive sampling, the ranges and distributions of concentrations in these subsets of data were similar. Some uncertainty is introduced by the limited size and representation of the data set (n = 151 homes in Windsor, Hamilton, Trois-Rivières, Québec, Saskatoon and various locations in the Northwest Territories), lack of random sampling of the homes and involvement of volunteers.

Although it contributes less to total exposure, there is a high degree of confidence in the characterization of the concentrations of formaldehyde in ambient air in Canada, due to the magnitude and sensitivity of the relevant monitoring data. Analytical and sampling methodologies were optimum, all of the samples were analyzed by a single specialized laboratory, and the effects of diurnal variation were minimized by the 24-hour sampling duration. The data set is large (n = 2819) and reasonably current (i.e., 1990–1998), and the concentrations of formaldehyde are consistent with those reported for outdoor air in other Canadian and international studies. However, the locations of NAPS sites were not determined by a random sampling scheme, and a subset of only eight NAPS sites was selected. The data may also not be strictly representative of population exposure, since the air is sampled at elevations higher than the breathing zone at some sites and may be remote from populated areas. However, samples from Canada's three major urban centres (i.e., Montréal with two sites, Toronto and Vancouver) account for 54% of the 2819 samples, and samples from two sites in Windsor, Ontario, account for an additional 21% of the samples in this data set.

Uncertainty concerning the time spent indoors by Canadians is judged to be low, since the estimate is based on the most current Canadian data, the time–activity data were obtained based on a random sampling scheme, and analysis of the data involved population weighting. However, the same mean time spent outdoors is assumed for Canadians of all age groups and in all regions of the country, a normal distribution is assumed for the hours per day spent outdoors, and the variance of the assumed normal distribution is also assumed (i.e., standard deviation of 2).

The degree of uncertainty concerning the formaldehyde content of food currently consumed by Canadians is sufficiently high so as to preclude meaningful estimation of exposure from this source, except as a basis for determining potential relative proportions of total intake from various media. Identified data on concentrations in this medium are restricted to a small number of food samples collected in other countries, sometimes in early studies for which there is some suspicion of production of formaldehyde due to the relatively high temperatures and acidic reagents employed.

There are no indications that food items were selected on a random basis and often no indication whether the reported concentrations reflect formaldehyde content in the food as consumed. Due to its high volatility, the formaldehyde content would be expected to be reduced during processing and cooking. Formaldehyde is not expected to partition into the fatty compartments of foods, and direct contact of formaldehyde in food applications is very limited. Also, while there is some suggestion that formaldehyde is present in food in bound (unavailable) form, data to substantiate this contention were not identified.

There is a moderate degree of certainty that consumption of drinking water does not contribute significantly to the daily intake of formaldehyde by Canadians, since formaldehyde is relatively unstable in water. However, no data concerning the range and distribution of concentrations of formaldehyde in Canadian drinking water were identified.

With respect to toxicity, the degree of confidence that critical effects are well characterized is high. A relatively extensive database in both humans and animals indicates that critical effects occur at the initial site of exposure to this substance. The database in humans is also sufficiently robust to serve as a basis for confident conclusion concerning the consistently lowest levels at which effects (i.e., sensory irritation) occur, although additional investigation of an unconfirmed report of effects on respiratory function in children exposed to lower levels of formaldehyde is desirable.

The degree of confidence in the database that supports an obligatory role of regenerative proliferation in the induction of nasal tumours in rats is moderate to high, although the mechanism of carcinogenicity of formaldehyde is unclear. Although the biologically motivated case-specific model for estimation of cancer risks is clearly preferred due to incorporation of as many biological data as possible, there are a number of uncertainties described in more detail in CIIT (1999) and summarized briefly here, although sensitivity analyses were not conducted. For dosimetry, sources of uncertainty for which sensitivity analyses would have been appropriate include the use of individual rat, primate and human nasal anatomies as representative of the general population, the use of a typical-path human lung structure to represent people with compromised lungs, the sizes of specific airways, the use of a symmetric Weibel model for the lung, the estimation of the location and extent of squamous and olfactory epithelium and of mucus- and non-mucus-coated nasal regions in the human, and the values of mass transfer and dispersion coefficients. The lack of human data on formaldehyde-related changes in the values of key parameters of the clonal growth model accounts for much of its uncertainty.

In order to better define the mode of action of induction of tumours, elaboration of the quantitative relationship between DPX and mutation and the time course of loss of DNA–protein crosslinks is desirable. Additional characterization of the shape of the concentration–response relationship for regenerative proliferative response would also be informative.

For Priority Substances where the induction of cancer through direct interaction with genetic material cannot be ruled out and available data are inadequate as a basis for development of biologically motivated case-specific models, cancer potency is estimated based on empirical modelling of experimental data within or close to the experimental range, as described above (Section 3.3.3). Estimates of exposure are then compared with these quantitative estimates of carcinogenic potency (Exposure Potency Index) to characterize risk and provide guidance in establishing priorities for further action (i.e., analysis of options to reduce exposure) (Health Canada, 1994) under CEPA 1999. While the biologically motivated case-specific model is clearly preferred as a basis for characterization of exposure–response for cancer for formaldehyde due to its incorporation of as many of the biological data as possible, the priority for investigation of options to reduce exposure based on default methodology is presented here for comparison.

Utilization of this default approach in the case of formaldehyde would indicate that probabilistic estimates of the 24-hour median, mean and 97.5th percentile concentrations of formaldehyde in air in Canada (generally and for a worst-case site) would be approximately 327-, 263- and 98-fold lower, respectively, than the maximum likelihood estimate of the carcinogenic potency (i.e., TC_{05} = 9.5 mg/m^3)[4] derived from a carcinogenesis bioassay in rats (Monticello *et al.*, 1996). Overall, based upon these Exposure Potency Indices (ranging from 3×10^{-3} to 1.0×10^{-2}), the priority for the investigation of options to reduce exposure to formaldehyde in air would have been considered to be high.

3.4 Conclusions

CEPA 1999 64(a): Based on analyses of worst-case situations that are likely to be encountered in Canada, risk quotients for water and air are less than 1. The environmental risks associated with concentrations of formaldehyde likely to be found in Canada therefore appear to be low. Therefore, available data indicate that it is unlikely that formaldehyde is entering or may enter the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity, and it is not considered to be "toxic" as defined in CEPA 1999 Paragraph 64(a).

CEPA 1999 64(b): Formaldehyde is not involved in depletion of stratospheric ozone and likely does not contribute significantly to climate change. Because of its reactivity and abundance in air, formaldehyde contributes, along with other reactive volatile organic chemicals, to the formation of tropospheric ozone. Therefore, based on available data, formaldehyde is entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger to the environment on which life depends, and it is considered to be "toxic" as defined in CEPA 1999 Paragraph 64(b).

CEPA 1999 64(c): Although other factors (such as sustained cellular proliferation) play an important role, there is likely a genetic component (i.e., mutation, for which DNA–protein crosslinks serve as a marker for potential) in the induction of tumours following the inhalation of formaldehyde. Therefore, formaldehyde is considered to be "toxic" as defined in Paragraph 64(c) of CEPA 1999. For compounds where the induction of cancer through direct interaction with genetic material cannot be ruled out, this approach is consistent with the objective that exposure be reduced wherever possible and obviates the need to establish an arbitrary "*de minimis*" level of risk for the determination of "toxic" under CEPA 1999. However, based on comparison of risks of cancer estimated on the basis of a biologically motivated case-specific model with calculated exposure in air of the general population in Canada, the priority for investigation of options to reduce exposure on the basis of carcinogenicity is considered to be low. While the majority of the population is exposed to concentrations of formaldehyde less than those associated with sensory irritation, continued investigation of options to reduce exposure to formaldehyde in indoor air is recommended as part of an overall program to reduce exposure to other aldehydes considered to be "toxic" under Paragraph 64(c) of CEPA 1999.

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[4] Concentration of formaldehyde causing a 5% increase in tumour incidence over background.

Overall conclusion: Based on critical assessment of relevant information, formaldehyde is considered to be "toxic" as defined in Section 64 of CEPA 1999.

3.5 Considerations for follow-up (further action)

Formaldehyde contributes to the photochemical formation of ground-level ozone. It is recommended that key sources of formaldehyde be addressed, therefore, as part of management plans for volatile organic chemicals that contribute to the formation of ground-level ozone. While indications are that concentrations currently in air and water are not causing environmental harm to biota, continued and improved monitoring at sites likely to release formaldehyde are desirable, notably with regards to industrial uses for resins and for fertilizers as well as releases from pulp and paper mills.

Although the priority for investigation of options to reduce exposure in the general environment is generally considered to be low, in relation to carcinogenic potential, in some indoor locations, concentrations are only slightly lower than, and may even approach, the level associated with signs of eye and respiratory tract sensory irritation in humans. Therefore, it is recommended that continued investigation of options to reduce exposure to formaldehyde in indoor air be considered under the authority of acts other than CEPA 1999 as part of an overall program to reduce exposure to other aldehydes (e.g., acrolein, acetaldehyde) in indoor air deemed to be "toxic" under Paragraph 64(c) of CEPA 1999. Where the control of any identified sources falls within the authority of an Act other than CEPA 1999, the results of these investigations should be forwarded to the appropriate authority for further consideration.

4.0 REFERENCES

Adams, D.O., T.A. Hamilton, L.D. Lauer and J.H. Dean. 1987. The effect of formaldehyde exposure upon the mononuclear phagocyte system of mice. Toxicol. Appl. Pharmacol. 88: 165–174.

Alberta Environmental Protection. 1996. Personal communication from G. Dinwoodie. Chemical Assessment and Management Division.

Alexandersson, R. and G. Hedenstierna. 1988. Respiratory hazards associated with exposure to formaldehyde and solvents in acid-curing paints. Arch. Environ. Health 43: 222–227.

Alexandersson, R. and G. Hedenstierna. 1989. Pulmonary function in wood workers exposed to formaldehyde: a prospective study. Arch. Environ. Health 44: 5-11.

Altshuller, A.P. and I.R. Cohen. 1964. Atmospheric photooxidation of the ethylene nitric oxide system. Int. J. Air Water Pollut. 8: 611–632.

Andersen, I. and L. Mølhave. 1983. Controlled human studies with formaldehyde. *In*: J.E. Gibson (ed.), Formaldehyde toxicity. Hemisphere Publishing, Washington, D.C. pp. 155–165.

Andersen, M. 1999. Final report: Review of revised edition(s) of the formaldehyde hazard characterization and dose–response assessment. Colorado State University, Fort Collins, Colorado (unpublished).

Anderson, W.B., P.M. Huck, I.P. Douglas, J. Van Den Oever, B.C. Hutcheon, J.C. Fraser, S.Y. Jasim, R.J. Patrick, H.E. Donison and M.P. Uza. 1995. Ozone byproduct formation in three different types of surface water. *In*: Proceedings of the 1994 Water Quality Technology Conference, November 6–10, 1994, San Francisco, California. Vol. 2. American Water Works Association, Denver, Colorado. pp. 871–908.

Andjelkovich, D.A., C.M. Shy, M.H. Brown, D.B. Jansen and R.B. Richardson. 1994. Mortality of iron foundry workers. III. Lung cancer case–control study. J. Occup. Med. 36: 1301–1309.

Andjelkovich, D.A., D.B. Jansen, M.H. Brown, R.B. Richardson and F.J. Miller. 1995. Mortality of iron foundry workers. IV. Analysis of a subcohort exposed to formaldehyde. J. Occup. Environ. Med. 36: 1301–1309.

Appelman, L.M., R.A. Woutersen, A. Zwart, H.E. Falke and V.J. Feron. 1988. One-year inhalation toxicity study of formaldehyde in male rats with a damaged or undamaged nasal mucosa. J. Appl. Toxicol. 8: 85–90.

ARB (Air Resources Board). 1993. Acetaldehyde as a toxic air contaminant. Part A. Exposure assessment. Stationary Source Division, California Environmental Protection Agency. November.

Atkinson, R. 1985. Kinetics and mechanisms of the gas-phase reactions of the hydroxyl radicals with organic compounds under atmospheric conditions. Chem. Rev. 85: 69–201.

Atkinson, R. 1989. Atmospheric lifetimes and fate of acetaldehyde. Research Division, Air Resources Board, California Environmental Protection Agency; Statewide Air Pollution Research Center, University of California, Riverside, California (Contract No. A732-107).

Atkinson, R. 1990. Gas-phase tropospheric chemistry of organic compounds: A review. Atmos. Environ. 24A: 1–41.

Atkinson, R., S.M. Aschmann, E.C. Tuazon, J. Arey and B. Zielinska. 1989. Formation of 3-methylfuran from the gas-phase reaction of OH radicals with isoprene and the rate constant for its reaction with the OH radical. Int. J. Chem. Kinet. 21: 593–604.

Atkinson, R., J. Arey, S.M. Aschmann, W.D. Long, E.C. Tuazon and A.M. Winer. 1990. Lifetimes and fates of toxic air contaminants in California's atmosphere, March 1990. Air Resources Board, California Environmental Protection Agency (Contract No. A732-107).

Atkinson, R., J. Arey, W.P. Harger, E.S.C. Kwok and W.D. Long. 1993. Lifetimes and fates of toxic air contaminants in California's atmosphere, June 1993. Research Division, Air Resources Board, California Environmental Protection Agency (Contract No. A032-055).

ATSDR (Agency for Toxic Substances and Disease Registry). 1997. Toxicological profile for formaldehyde. Draft for public comment. Public Health Service, U.S. Department of Health and Human Services, Atlanta, Georgia. 364 pp.

ATSDR (Agency for Toxic Substances and Disease Registry). 1999. Toxicological profile for formaldehyde. Prepared by Syracuse Research Corporation for Public Health Service, U.S. Department of Health and Human Services, Atlanta, Georgia.

Baker, D.C. 1994. Projected emissions of hazardous air pollutants from a Shell coal gasification process-combined-cycle power plant. Fuel 73(7): 1082–1086.

Ballarin, C., F. Sarto, L. Giacomelli, G.B. Bartolucci and E. Clonfero. 1992. Micronucleated cells in nasal mucosa of formaldehyde-exposed workers. Mutat. Res. 280: 1–7.

Baraniak, Z., D.S. Nagpal and E. Neidert. 1988. Gas chromatographic determination of formaldehyde in maple syrup as 2,4-dinitrophenylhydrazone derivative. J. Assoc. Off. Anal. Chem. 71(4): 740–741.

Bardana, E.J., Jr. and A. Montanaro. 1991. Formaldehyde: an analysis of its respiratory, cutaneous, and immunologic effects. Ann. Allergy 66: 441–452.

Barker, J.R. and R.A. Shimabuku. 1992. Formaldehyde-contaminated fog effects on plant growth. Presented at the 85th Annual Meeting and Exhibition, June 21–26, 1992, Kansas City, Missouri. 13 pp. (Air and Waste Management Association Report 92-150.01).

Barrow, C.S., W.H. Steinhagen and J.F. Chang. 1983. Formaldehyde sensory irritation. *In*: J.E. Gibson (ed.), Formaldehyde toxicity. Hemisphere Publishing, Washington, D.C. pp. 16–25.

Bauchinger, M. and E. Schmid. 1985. Cytogenetic effects in lymphocytes of formaldehyde workers of a paper factory. Mutat. Res. 158: 195–199.

BCH (Bureau of Chemical Hazards). 1988. Report to the Federal–Provincial Working Group on Indoor Air Quality — Formaldehyde. Environmental Health Directorate, Department of National Health and Welfare, Ottawa, Ontario.

Berke, J.H. 1987. Cytologic examination of the nasal mucosa in formaldehyde-exposed workers. J. Occup. Med. 29: 681–684.

Bermudez, E. and L.L. Delehanty. 1986. The effects of *in vitro* formaldehyde treatment on the cells of the rat nasal epithelium. Environ. Mutagen. 8: 11.

Bertazzi, P.A., A. Pesatori, S. Guercilena, D. Consonni and C. Zocchetti. 1989. [Cancer risk among workers producing formaldehyde-based resins: extension of follow-up.] Med. Lav. 80: 111–122 (in Italian).

Betterton, E.A. and M.R. Hoffmann. 1988. Henry's law constants of some environmentally important aldehydes. Environ. Sci. Technol. 22: 361–367.

Bhalla, D.K., V. Mahavni, T. Nguyen and T. McClure. 1991. Effects of acute exposure to formaldehyde on surface morphology of nasal epithelia in rats. J. Toxicol. Environ. Health 33: 171–188.

Bhatt, H.S., S.B. Lober and B. Combes. 1988. Effect of glutathione depletion on aminopyrine and formaldehyde metabolism. Biochem. Pharmacol. 37: 1581–1589.

BIBRA (BIBRA Toxicology International). 1994. Formaldehyde. Contract report prepared for Health Canada. 181 pp.

Bierbach, A., I. Barnes, K.H. Becker, B. Klotz and E. Wiesen. 1994. OH-radical initiated degradation of aromatic hydrocarbons. *In*: G. Angeletti and G. Restelli (eds.), Physico-chemical behaviour of atmospheric pollutants. Proceedings of the 6th European Symposium, Varese, October 18–22, 1993. Commission of the European Community, Brussels. pp. 129–136 (CEC Report EUR 15609/1 EN).

Billings, R.E., R.H. Ku, M.E. Brower, C.E. Dallas and J.C. Theiss. 1984. Disposition of formaldehyde (CH_2O) in mice. Toxicologist 4: 29.

Bills, D., L. Marking and H. Chandler, Jr. 1977. Investigation in fish control. 73. Formalin: Its toxicity to nontarget aquatic organisms, persistence and counteraction. Fish and Wildlife Service, U.S. Department of the Interior, Washington, D.C. pp. 1–7.

Birdsong, C.L. and J.V. Avault, Jr. 1971. Toxicity of certain chemicals to juvenile pompano. Prog. Fish Cult. 33(2): 76–80.

Blair, A. and P.A. Stewart. 1994. Comments on the Sterling and Weinkam analysis of data from the National Cancer Institute formaldehyde study. Am. J. Ind. Med. 25: 603–606.

Blair, A., P. Stewart, M. O'Berg, W. Gaffey, J. Walrath, J. Ward, R. Bales, S. Kaplan and D. Cubit. 1986. Mortality among industrial workers exposed to formaldehyde. J. Natl. Cancer Inst. 76: 1071–1084.

Blair, A., P.A. Stewart, R.N. Hoover, J.F. Fraumeni, J. Walrath, M. O'Berg and W. Gaffey. 1987. Cancers of the nasopharynx and oropharynx and formaldehyde exposure. J. Natl. Cancer Inst. 78: 191–192.

Blair, A., P.A. Stewart and R.N. Hoover. 1990a. Mortality from lung cancer among workers employed in formaldehyde industries. Am. J. Ind. Med. 17: 683–699.

Blair, A., R. Saracci, P.A. Stewart, R.B. Hayes and C. Shy. 1990b. Epidemiologic evidence on the relationship between formaldehyde exposure and cancer. Scand. J. Work Environ. Health 16: 381–393.

Blair, A., A. Linos, P.A. Stewart, L.F. Burmeister, R. Gibson, G. Everett, L. Schuman and K.P. Cantor. 1993. Evaluation of risks for non-Hodgkin's lymphoma by occupation and industry exposures from a case–control study. Am. J. Ind. Med. 23: 301–312.

BND (Bureau of Nonprescription Drugs). 1994. Personal communication from R. Green, BND, Health Canada, to R. Liteplo, Priority Substances Section, Bureau of Chemical Hazards, Health Canada, Ottawa, Ontario, regarding registration of formulations containing formaldehyde in the Cosmetic Notification System database.

Bobra, A. and D. Mackay. 1999. Personal communication to Commercial Chemicals Evaluation Branch, Environment Canada, Hull, Quebec.

Boffetta, P., S.D. Stellman and L. Garfinkel. 1989. A case–control study of multiple myeloma nested in the American Cancer Society prospective study. Int. J. Cancer 43: 554–559.

Bond, G.G., G.H. Flores, R.J. Shellenberger, J.B. Cartmill, W.A. Fishbeck and R.R. Cook. 1986. Nested case–control study of lung cancer among chemical workers. Am. J. Epidemiol. 124: 53–66.

Boysen, M., E. Zadig, V. Digernes, V. Abeler and A. Reith. 1990. Nasal mucosa in workers exposed to formaldehyde: a pilot study. Br. J. Ind. Med. 47: 116–121.

Bracamonte, B.G., F.J. Ortiz de Frutos and L.I. Diez. 1995. Occupational allergic contact dermatitis due to formaldehyde and textile finish resins. Contact Dermatitis 33: 139–140.

Bringmann, G. and R. Kühn. 1980a. Comparison of the toxicity thresholds of water pollutants to bacteria, algae and protozoa in the cell multiplication inhibition test. Water Res. 14: 231–241.

Bringmann, G. and R. Kühn. 1980b. [Determination of the harmful effect on protozoa of substances endangering water quality. II. Bacteria-consuming ciliates.] Z. Wasser Abwasser Forsch. 1: 26–31 (in German).

Bringmann, G., R. Kühn and A. Winter. 1980. Determination of biological damage from water pollutants to protozoa. III. Saprozoic flagellates. Z. Wasser Abwasser Forsch. 13(5): 170–173.

British Columbia Ministry of Health. 1998. Data from Ministry of Health web site (www.cctc.ca/bcreorts/results.htm) regarding emission factors of toxic chemicals from mainstream and sidestream smoke from 11 brands of Canadian cigarettes. Victoria, British Columbia.

Broder, I., P. Corey, P. Cole, M. Lipa, S. Mintz and J.R. Nethercott. 1988. Comparison of health of occupants and characteristics of houses among control homes and homes insulated with urea formaldehyde foam. II. Initial health and house variables and exposure–response relationships. Environ. Res. 45: 156–178.

Brownson, R.C., M.C.R. Alavanja and J.C. Chang. 1993. Occupational risk factors for lung cancer among nonsmoking women: a case–control study in Missouri (United States). Cancer Causes Control 4: 449–454.

Brunn, W. and H. Klostermeyer. 1984. [Detection and determination of formaldehyde in foods.] Lebensmittelchem.Gerichtl. Chem. 38: 16–17 (in German) [cited in Buckley *et al.*, 1988].

Buckley, K.E., L.J. Fisher and V.G. Mackay. 1986. Electron capture gas chromatographic determination of traces of formaldehyde in milk as the 2,4-dinitrophenylhydrazone. J. Assoc. Off. Anal. Chem. 69(4): 655–657.

Buckley, K.E., L.J. Fisher and V.G. Mackay. 1988. Levels of formaldehyde in milk, blood, and tissues of dairy cows and calves consuming formalin-treated whey. J. Agric. Food Chem. 36: 1146–1150.

Bunce, N. 1996. Atmospheric properties of substances on the Priority Substances List (PSL2) — Report to Environment Canada. University of Guelph, Guelph, Ontario (unpublished).

Burridge, T.R., T. Lavery and P.K.S. Lam. 1995a. Effects of tributyltin and formaldehyde on the germination and growth of *Phyllospora comosa* (Labillardiere) C. Agardh (Phaeophyta: Fucales). Bull. Environ. Contam. Toxicol. 55: 525–532.

Burridge, T.R., T. Lavery and P.K.S. Lam. 1995b. Acute toxicity tests using *Phyllospora comosa* (Labillardiere) C. Agardh (Phaeophyta: Fucales) and *Allorchestes compressa* Dana (Crustacea: Amphipoda). Bull. Environ. Contam. Toxicol. 55: 621–628.

Callas, P.W., H. Pastides and D.W. Hosmer. 1996. Lung cancer mortality among workers in formaldehyde industries. J. Occup. Environ. Med. 38: 747–748.

Calvert, J.G., J.A. Kerr, K.L. Demerjian and R.D. McQuigg. 1972. Photolysis of formaldehyde as a hydrogen atom source in the lower atmosphere. Science 175: 751–752.

Cantoni, C., E. Milva and M. Bazzani. 1987. [Formaldehyde content in foods of animal origin.] Ind. Aliment. 26(2): 123–126, 132 (in Italian).

Carmichael, G. 1983. Use of formalin to separate tadpoles from large-mouth bass fingerlings after harvesting. Prog. Fish Cult. 45: 105–106.

Carter, W.P.L. 1994. Development of ozone reactivity scales for volatile organic compounds. J. Air Waste Manage. Assoc. 44: 881–899.

Carter, W.P.L., J.A. Pierce, D. Luo and I.L. Malkina. 1995. Environmental chamber study of maximum incremental reactivities of volatile organic compounds. Atmos. Environ. 29: 2499–2511.

Casanova, M. and H.d'A. Heck. 1987. Further studies of the metabolic incorporation and covalent binding of inhaled [^{3}H]- and [^{14}C]formaldehyde in Fischer-344 rats: effects of glutathione depletion. Toxicol. Appl. Pharmacol. 89: 105–121.

Casanova, M., D.F. Deyo and H.d'A. Heck. 1989. Covalent binding of inhaled formaldehyde to DNA in the nasal mucosa of Fischer 344 rats: analysis of formaldehyde and DNA by high-performance liquid chromatography and provisional pharmacokinetic interpretation. Fundam. Appl. Toxicol. 12: 397–417.

Casanova, M., K.T. Morgan, W.H. Steinhagen, J.I. Everitt, J.A. Popp and H.d'A. Heck. 1991. Covalent binding of inhaled formaldehyde to DNA in the respiratory tract of rhesus monkeys: pharmacokinetics, rat-to-monkey interspecies scaling, and extrapolation to man. Fundam. Appl. Toxicol. 17: 409–428.

Casanova, M., K.T. Morgan, E.A. Gross, O.R. Moss and H.d'A. Heck. 1994. DNA–protein cross-links and cell replication at specific sites in the nose of F344 rats exposed subchronically to formaldehyde. Fundam. Appl. Toxicol. 23: 525–536.

Cassee, F.R., J.P. Groten and V.J. Feron. 1996. Changes in the nasal epithelium of rats exposed by inhalation to mixtures of formaldehyde, acetaldehyde, and acrolein. Fundam. Appl. Toxicol. 29: 208–218.

CEU (Commission of the European Union). 1995. Technical guidance document on environmental risk assessment for existing substances in the context of Commission regulation XX/94 in accordance with Council Regulation (EEC) No. 793/93 on the evaluation and control of existing substances. Chap. 3. Prepared by Chemicals Group of Umweltbundesamt, Berlin, under Contract B4-3040-93-663/AO. 82 pp.

Chan, G.S., M. Scafe and S. Emami. 1992. Cemeteries and groundwater: An examination of the potential contamination of groundwater by preservatives containing formaldehyde. Water Resources Branch, Ontario Ministry of the Environment.

Chang, J.C.F., W.H. Steinhagen and C.S. Barrow. 1981. Effect of single or repeated formaldehyde exposure on minute volume of B6C3F1 mice and F-344 rats. Toxicol. Appl. Pharmacol. 61: 451–459.

Chapman, P.M., A. Fairbrother and D. Brown. 1998. A critical evaluation of safety (uncertainty) factors for ecological risk assessment. Environ. Toxicol. Chem. 17(1): 99–108.

Chou, C.C. and S.S. Que Hee. 1992. Microtox EC$_{50}$ values for drinking water by-products produced by ozonolysis. Ecotoxicol. Environ. Saf. 23: 355–363.

CIIT (Chemical Industry Institute of Toxicology). 1999. Formaldehyde: Hazard characterization and dose–response assessment for carcinogenicity by the route of inhalation. Revised edition. Research Triangle Park, North Carolina.

Collins, J.J., J.C. Caporossi and H.M.D. Utidjian. 1988. Formaldehyde exposure and nasopharyngeal cancer: re-examination of the National Cancer Institute study and an update of one plant. J. Natl. Cancer Inst. 80: 376–377.

Collins, J.J., J.F. Acquavella and N.A. Esmen. 1997. An updated meta-analysis of formaldehyde exposure and upper respiratory cancers. J. Occup. Environ. Med. 39: 639–651.

Cosma, G.N., R. Jamasbi and A.C. Marchok. 1988. Growth inhibition and DNA damage induced by benzo[*a*]pyrene and formaldehyde in primary cultures of rat tracheal epithelial cells. Mutat. Res. 201: 161–168.

Craft, T.R., E. Bermudez and T.R. Skopek. 1987. Formaldehyde mutagenesis and formation of DNA protein crosslinks in human lymphoblasts *in vitro*. Mutat. Res. 176: 147–155.

Crosby, R.M., K.K. Richardson, T.R. Craft, K.B. Benforado, H.L. Liber and T.R. Skopek. 1988. Molecular analysis of formaldehyde-induced mutations in human lymphoblasts and *E. coli*. Environ. Mol. Mutagen. 12: 155–166.

Cross, G.L.C. and V.H. Lach. 1990. The effects of controlled exposure to formaldehyde vapours on spores of *Bacillus globigii* nctc 10073. J. Appl. Bacteriol. 68(5): 461–470.

Crump, D.R., C.W.F. Yu, R.W. Squire and M. Atkinson. 1996. Small chamber methods for characterizing formaldehyde emission from particleboard. *In*: B.A. Tichenor (ed.), Characterizing sources of indoor air pollution and related sink effects. American Society for Testing and Materials, Philadelphia, Pennsylvania. pp. 211–214 (ASTM Special Technical Publication 1287).

Daisey, J.M., K.R.R. Mahanama and A.T. Hodgson. 1994. Toxic volatile organic compounds in environmental tobacco smoke: Emission factors for modelling exposures of California populations. Prepared for Research Division, Air Resources Board, California Environmental Protection Agency, Sacramento, California. 109 pp. (Contract No. A133-186).

Dalbey, W.E. 1982. Formaldehyde and tumours in hamster respiratory tract. Toxicology 24: 9–14.

Dallas, C.E., M.J. Scott, J.B. Ward, Jr. and J.C. Theiss. 1992. Cytogenetic analysis of pulmonary lavage and bone marrow cells of rats after repeated formaldehyde inhalation. J. Appl. Toxicol. 12: 199–203.

Dann, T. 1997. Excel™ file titled "Formaldehyde concentration (µg/m^3) by sampling day" regarding National Air Pollution Surveillance (NAPS) program data for formaldehyde for four urban and four suburban sites for the period 1989–1996. Received September 2, 1997, from River Road Environmental Technology Centre, Environment Canada, Ottawa, Ontario.

Dann, T. 1999. Excel™ file titled "Time series for formaldehyde" regarding National Air Pollution Surveillance (NAPS) program data for formaldehyde for the period 1997–1998. Received December 22, 1999, from River Road Environmental Technology Centre, Environment Canada, Ottawa, Ontario.

Dann, T. and P. Summers 1997. Ground-level ozone and its precursors, 1980–1993. Canadian 1996 NO_x/VOC Science Assessment, Report of the Data Analysis Working Group. Multistakeholder NO_x/VOC Science Program.

Day, J.H., R.E.M. Lees, R.H. Clark and P.L. Pattee. 1984. Respiratory response to formaldehyde and off-gas of urea formaldehyde foam insulation. Can. Med. Assoc. J. 131: 1061–1065.

Dean, J. 1985. Lange's handbook of chemistry. 13th edition. McGraw-Hill, New York, N.Y.

Dean, J.H., L.D. Lauer, R.V. House, M.J. Murray, W.S. Stillman, R.D. Irons, W.H. Steinhagen, M.C. Phelps and D.O. Adams. 1984. Studies of immune function and host resistance in $B6C3F_1$ mice exposed to formaldehyde. Toxicol. Appl. Pharmacol. 72: 519–529.

de Andrade, J.B., M.S. Bispo, M.V. Rebouças, M.L.S.M. Carvalho and H.L.C. Pinheiro. 1996. Spectrofluorimetric determination of formaldehyde in liquid samples. Am. Lab. 28(12): 56–58.

Decisioneering, Inc. 1996. Crystal Ball Version 4.0. User manual. Denver, Colorado. 286 pp.

Deneer, J.W., W. Seinen and W. Hermens. 1988. The acute toxicity of aldehydes to the guppy. Aquat. Toxicol. 12: 185–192.

Dennis, C. and H. Gaunt. 1974. Effect of formaldehyde on fungi from broiler houses. J. Appl. Bacteriol. 37: 595–601.

De Serves, C. 1994. Gas phase formaldehyde and peroxide measurements in the Arctic atmosphere. J. Geophys. Res. 99(D12): 25 391–25 398.

DMER (Don Mackay Environmental Research) and AEL (Angus Environmental Limited). 1996. Pathways analysis using fugacity modelling of formaldehyde for the second Priority Substances List. Prepared for Chemicals Evaluation Division, Commercial Chemicals Evaluation Branch, Environment Canada, by DMER, Peterborough, Ontario, and AEL, Don Mills, Ontario. March.

Dobiás, L., J. Hanzl, P. Rössner, L. Janča, H. Rulíšková, S. Andělová and H. Klementová. 1988. [Evaluation of the clastogenic effect of formaldehyde in children in preschool and school facilities.] Cesk. Hyg. 33: 596–604 (in Czechoslovakian).

Dobiás, L., L. Janča, I. Lochman and A. Lochmanova. 1989. Genotoxic action of formaldehyde in exposed children. Mutat. Res. 216: 310.

Dong, S. and P.K. Dasgupta. 1986. Solubility of gaseous formaldehyde in liquid water and generation of trace standard gaseous formaldehyde. Environ. Sci. Technol. 20: 637–640.

Eberhardt, M.A. and J. Sieburth. 1985. A colorimetric procedure for the determination of aldehydes in seawater and in cultures of methylotrophic bacteria. Mar. Chem. 17: 199–212.

Ebner, H. and D. Kraft. 1991. Formaldehyde-induced anaphylaxis after dental treatment? Contact Dermatitis 24: 307–309.

Edling, C., B. Jarvholm, L. Andersson and O. Axelson. 1987. Mortality and cancer incidence among workers in an abrasive manufacturing industry. Br. J. Ind. Med. 44: 57–59.

Edling, C., H. Hellquist and L. Ödkvist. 1988. Occupational exposure to formaldehyde and histopathological changes in the nasal mucosa. Br. J. Ind. Med. 45: 761–765.

EHD (Environmental Health Directorate). 1998. Exposure factors for assessing total daily intake of Priority Substances by the general population of Canada. Priority Substances Section, EHD, Health Canada, Ottawa, Ontario (unpublished).

El Sayed, F., D. Seite-Bellezza, B. Sans, P. Bayle-Lebye, M.C. Marguery and J. Baziex. 1995. Contact urticaria from formaldehyde in a root-canal dental paste. Contact Dermatitis 33: 353.

Environment Canada. 1985. Formaldehyde: Environmental and technical information for problem spills (EnviroTIPS).

Environment Canada. 1995. Technical briefing note on composite wood panels. Report prepared for Environmental Choice Program. Ottawa, Ontario. May 18.

Environment Canada. 1996. Summary report — 1994. National Pollutant Release Inventory (NPRI). Pollution Data Branch, Hull, Quebec.

Environment Canada. 1997a. Environmental assessments of Priority Substances under the *Canadian Environmental Protection Act*. Guidance manual version 1.0 — March 1997. Chemicals Evaluation Division, Commercial Chemicals Evaluation Branch, Hull, Quebec (Environmental Protection Series EPS/2/CC/3E).

Environment Canada. 1997b. Notice respecting the second Priority Substances List and di(2-ethylhexyl) phthalate. *Canada Gazette*, Part I, February 15, 1997. pp. 366–368.

Environment Canada. 1997c. Results of the CEPA Section 16 Notice to Industry respecting the second Priority Substances List and di(2-ethylhexyl) phthalate. Use Patterns Section, Commercial Chemicals Evaluation Branch, Hull, Quebec.

Environment Canada. 1997d. VOC emissions survey of adhesives, sealants and adhesive tape manufacturers in Canada (draft). Report prepared for Pollution Data Branch, Hull, Quebec.

Environment Canada. 1999a. *Canadian Environmental Protection Act* — Priority Substances List — Supporting document for the environmental assessment of formaldehyde. Commercial Chemicals Evaluation Branch, Hull, Quebec.

Environment Canada. 1999b. Summary report — 1997. National Pollutant Release Inventory (NPRI). *Canadian Environmental Protection Act*. Hull, Quebec.

Environment Canada and Health Canada. 2000. Publication after assessment of a substance — formaldehyde — specified on the Priority Substances List (Subsection 77(1) of the *Canadian Environmental Protection Act, 1999*). *Canada Gazette*, Part I, July 22, 2000. pp. 2303–2305.

Etkin, D.S. 1996. Volatile organic compounds in indoor environments. Cutter Information Corp., Arlington, Massachusetts. 426 pp.

Feeley, M. 1996. Personal communication. Chemical Health Hazard Assessment Division, Bureau of Chemical Safety, Food Directorate, Health Canada, Ottawa, Ontario. June 1996.

Feinman, S.E. (ed.). 1988. Formaldehyde sensitivity and toxicity. CRC Press, Boca Raton, Florida.

Feron, V.J., J.P. Bruyntjes, R.A. Woutersen, H.R. Immel and L.M. Appelman. 1988. Nasal tumours in rats after short-term exposure to a cytotoxic concentration of formaldehyde. Cancer Lett. 39: 101–111.

Figley, D.A. and J.T. Makohon. 1993. Efficacy of post-manufacture surface coatings to reduce formaldehyde emissions from composite wood products. *In*: Proceedings of the 86th Annual Meeting of the Air and Waste Management Association, Denver, Colorado, June 1993. Vol. 11A. Health risk: human and ecological. 11 pp. (Paper No. 93-MP-3.01).

Fisher, P.W., J.A. Foster and K. Deb. 1991. Development of toxic air pollutant emissions for thirteen pulp and paper mills in Wisconsin. TAPPI Proceedings 1991 Environmental Conference. Technical Association of the Pulp and Paper Industry, Atlanta, Georgia. pp. 469–481.

Fleig, I., N. Petri, W.G. Stocker and A.M. Theiss. 1982. Cytogenetic analysis of blood lymphocytes of workers exposed to formaldehyde in formaldehyde manufacturing and processing. J. Occup. Med. 24: 1009–1012.

Fletcher, J.S., F.L. Johnson and J.C. McFarlane. 1990. Influence of greenhouse versus field testing and taxonomic differences on plant sensitivity to chemical treatment. Environ. Toxicol. Chem. 9: 769–776.

Florence, E. and D.F. Milner. 1981. Determination of free and loosely protein-bound formaldehyde in the tissues of pigs fed formalin-treated skim milk as a protein supplement. J. Sci. Food Agric. 32: 288–292.

Flyvholm, M.-A. and P. Andersen. 1993. Identification of formaldehyde releasers and occurrence of formaldehyde and formaldehyde releasers in registered chemical products. Am. J. Ind. Med. 24: 533–552.

Flyvholm, M.-A. and T. Menné. 1992. Allergic contact dermatitis from formaldehyde. Contact Dermatitis 27: 27–36.

Fontignie-Houbrechts, N. 1981. Genetic effects of formaldehyde in the mouse. Mutat. Res. 88: 109–114.

Fowler, J.F., S.M. Skinner and D.V. Belsito. 1992. Allergic contact dermatitis from formaldehyde resins in permanent press clothing: An underdiagnosed cause of generalized dermatitis. J. Am. Acad. Dermatol. 27: 962–968.

Fredberg, J.J., M.E. Wohl, G.M. Glass and H.L. Dorkin. 1980. Airway area by acoustic reflections measured at the mouth. J. Appl. Physiol. 48(5): 749–758.

Gardner, M.J., B. Pannett, P.D. Winter and A.M. Cruddas. 1993. A cohort study of workers exposed to formaldehyde in the British chemical industry: an update. Br. J. Ind. Med. 50: 827–834.

Gay, B.W., Jr. and J.J. Bufalini. 1971. Nitric acid and the nitrogen balance of irradiated hydrocarbons in the presence of oxides of nitrogen. Environ. Sci. Technol. 5: 422–425.

Gérin, M., J. Siemiatycki, L. Nadon, R. Dewar and D. Krewski. 1989. Cancer risks due to occupational exposure to formaldehyde: results of a multi-site case–control study in Montreal. Int. J. Cancer 44: 53–58.

Gocke, E., M.-T. King, K. Eckhardt and D. Wild. 1981. Mutagenicity of cosmetics ingredients by the European Communities. Mutat. Res. 90: 91–109.

Godish, T. 1988. Residential formaldehyde contamination: sources and levels. Comments Toxicol. 2(3): 115–134.

Godish, T. 1989. Formaldehyde exposures from tobacco smoke: a review. Am. J. Public Health 79(8): 1044–1045.

Government of Canada. 1982. Report on urea formaldehyde foam insulation. Minutes of proceedings and evidence of the Standing Committee on Health, Welfare and Social Affairs (Committee Chairman: Marcel Roy). Canadian Government Publishing Centre, Hull, Quebec. December 1982.

Green, D.J., L.R. Sauder, T.J. Kulle and R. Bascom. 1987. Acute response to 3.0 ppm formaldehyde in exercising healthy nonsmokers and asthmatics. Am. Rev. Respir. Dis. 135: 1261–1266.

Green, D.J., R. Bascom, E.M. Healey, J.R. Hebel, L.R. Sauder and T.J. Kulle. 1989. Acute pulmonary response in healthy, nonsmoking adults to inhalation of formaldehyde and carbon. J. Toxicol. Environ. Health 28: 261–275.

Grosjean, D. 1982. Formaldehyde and other carbonyls in Los Angeles ambient air. Environ. Sci. Technol. 16: 254–262.

Grosjean, D. 1990a. Atmospheric chemistry of toxic contaminants. 2. Saturated aliphatics: acetaldehyde, dioxane, ethylene glycol ethers, propylene oxide. J. Air Waste Manage. Assoc. 40(11): 1522–1531.

Grosjean, D. 1990b. Gas-phase reaction of ozone with 2-methyl-2-butene: Dicarbonyl formation from Criegee biradicals. Environ. Sci. Technol. 24: 1428–1432.

Grosjean, D. 1991a. Atmospheric chemistry of toxic contaminants. 4. Saturated halogenated aliphatics: methyl bromide, epichlorhydrin, phosgene. J. Air Waste Manage. Assoc. 41(1): 56–61.

Grosjean, D. 1991b. Atmospheric chemistry of toxic contaminants. 5. Unsaturated halogenated aliphatics: Allyl chloride, chloroprene, hexachlorocyclopentadiene, vinylidene chloride. J. Air Waste Manage. Assoc. 41(2): 182–189.

Grosjean, D. 1991c. Atmospheric fate of toxic aromatic compounds. Sci. Total Environ. 100: 367–414.

Grosjean, D., R. Swanson and C. Ellis. 1983. Carbonyls in Los Angeles air: contribution of direct emissions and photochemistry. Sci. Total Environ. 28: 65–85.

Grosjean, D., E. Grosjean and E.L. Williams II. 1993a. Atmospheric chemistry of unsaturated alcohols. Environ. Sci. Technol. 27: 2478–2485.

Grosjean, D., E. Grosjean and E.L. Williams. 1993b. The reaction of ozone with MPAN, $CH_2=C(CH_3)C(O)OONO_2$. Environ. Sci. Technol. 27: 2548–2552.

Grosjean, E., D. Grosjean and J.H. Seinfeld. 1996a. Atmospheric chemistry of 1-octene, 1-decene cyclohexene: gas-phase carbonyl and peroxyacyl nitrate products. Environ. Sci. Technol. 30(3): 1038–1047.

Grosjean, E., J.B. de Andrade and D. Grosjean. 1996b. Carbonyl products of the gas-phase reaction of ozone with simple alkenes. Environ. Sci. Technol. 30(3): 975–983.

Guerin, M.R., R.A. Jenkins and B.A. Tomkins. 1992. The chemistry of environmental tobacco smoke: composition and measurement. Lewis Publishers, Boca Raton, Florida.

Guski, M.E. and D.T. Raczynski. 1994. Evaluation of air toxic emissions and impacts from an urban wood waste to energy facility. 87th Annual Meeting and Exhibition, Air and Waste Management Association, Cincinnati, Ohio. 15 pp. (Presentation 94-RP130.04).

Haagen-Smit, A.J., E.E. Darley, M. Zaitlin, H. Hull and W.M. Noble. 1952. Investigation on injury to plants from air pollution in the Los Angeles area. Plant Physiol. 27: 18–34.

Hansch, C. and A. Leo. 1979. Substituent constants for correlation analysis in chemistry and biology. John Wiley and Sons, New York, N.Y.

Hansch, C. and A.J. Leo. 1981. MEDCHEM Project. Issue No. 19. Pomona College, Claremont, California.

Hansen, J. and J.H. Olsen. 1995. Formaldehyde and cancer morbidity among male employees in Denmark. Cancer Causes Control 6: 354–360.

Harley, R.A. and G.R. Cass. 1994. Modeling the concentrations of gas-phase toxic organic air pollutants: direct emissions and atmospheric formation. Environ. Sci. Technol. 28(1): 88–98.

Harving, H., J. Korsgaard, O.F. Pedersen, L. Mølhave and R. Dahl. 1990. Pulmonary function and bronchial reactivity in asthmatics during low-level formaldehyde exposure. Lung 168: 15–21.

Hatch, K.L. and H.I. Maibach. 1995. Textile dermatitis: an update (I). Resins, additives and fibers. Contact Dermatitis 32: 319–326.

Hayashi, T., C.A. Reece and T. Shibamoto. 1986. Gas chromatographic determination of formaldehyde in coffee via thiazolidine derivative. J. Assoc. Off. Anal. Chem. 69(1): 101–105.

Hayes, R.B., J.W. Raatgever, A. de Bruyn and M. Gerin. 1986. Cancer of the nasal cavity and paranasal sinuses, and formaldehyde exposure. Int. J. Cancer 37: 487–492.

Hayes, R.B., A. Blair, P.A. Stewart, R.F. Herrick and H. Mahar. 1990. Mortality of U.S. embalmers and funeral directors. Am. J. Ind. Med. 18: 641–652.

Health Canada. 1994. *Canadian Environmental Protection Act*. Human health risk assessment for Priority Substances. Ministry of Supply and Services, Ottawa, Ontario. 36 pp.

Health Canada. 1997. Health Canada 1994 Survey on Smoking in Canada. Chron. Dis. Can. 18(3). Laboratory Centre for Disease Control, Health Protection Branch, Ottawa, Ontario.

Health Canada. 1998. Report of Health Canada/U.S. EPA External Peer Review Workshop on Formaldehyde. Ottawa, Ontario (unpublished).

Health Canada. 1999. *Canadian Environmental Protection Act* — Supporting documentation — Health-related effects. Formaldehyde. Ottawa, Ontario (unpublished).

Health Canada. 2000. Draft supporting documentation for PSL2 assessments. Human exposure assessment for formaldehyde. Priority Substances Section, Health Protection Branch, Ottawa, Ontario. January 2000.

Heck, H.d'A. and M. Casanova. 1987. Isotope effects and their implications for the covalent binding of inhaled $[^3H]$- and $[^{14}C]$formaldehyde in the rat nasal mucosa. Toxicol. Appl. Pharmacol. 89: 122–134.

Heck, H.d'A. and M. Casanova. 1994. Nasal dosimetry of formaldehyde: Modelling site specificity and the effects of preexposure. Inhal. Toxicol. 6 (Suppl.): 159–175.

Heck, H.d'A., T.Y. Chin and M.C. Schmitz. 1983. Distribution of $[^{14}C]$formaldehyde in rats after inhalation exposure. *In*: J.E. Gibson (ed.), Formaldehyde toxicity. Hemisphere Publishing, Washington, D.C. pp. 26–37.

Heck, H.d'A., M. Casanova-Schmitz, P.B. Dodd, E.N. Schachter, T.J. Witek and T. Tosun. 1985. Formaldehyde (CH_2O) concentrations in the blood of humans and Fischer-344 rats exposed to CH_2O under controlled conditions. Am. Ind. Hyg. Assoc. J. 46: 1–3.

Heineman, E.F., J.H. Olsen, L.M. Pottern, M. Gomez, E. Raffn and A. Blair. 1992. Occupational risk factors for multiple myeloma among Danish men. Cancer Causes Control 3: 555–568.

Hellebust, J.A. 1974. Extracellular products. *In*: W.D.P. Stewart (ed.), Algal physiology and biochemistry. Blackwell Scientific Publications, Oxford, U.K. pp. 838–863.

Helms, D.R. 1964. The use of formalin to control tadpoles in hatchery ponds. M.Sc. Thesis, Southern Illinois University, Carbondale, Illinois. 28 pp.

Hemminki, K., P. Kyyrönen and M.-L. Lindbohm. 1985. Spontaneous abortions and malformations in the offspring of nurses exposed to anaesthetic gases, cytostatic drugs, and other potential hazards in hospitals, based on registered information of outcome. J. Epidemiol. Commun. Health 39: 141–147.

Herbert, F.A., P.A. Hessel, L.S. Melenka, K. Yoshida and M. Nakaza. 1994. Respiratory consequences of exposure to wood dust and formaldehyde of workers manufacturing oriented strand board. Arch. Environ. Health 49: 465–470.

Holly, E.A., D.A. Aston, D.K. Ahn and A.H. Smith. 1996. Intraocular melanoma linked to occupations and chemical exposures. Epidemiology 7: 55–61.

Holmström, M. and B. Wilhelmsson. 1988. Respiratory symptoms and pathophysiological effects of occupational exposure to formaldehyde and wood dust. Scand. J. Work Environ. Health 14: 306–311.

Holmström, M., B. Wilhelmsson and H. Hellquist. 1989a. Histological changes in the nasal mucosa in rats after long-term exposure to formaldehyde and wood dust. Acta Otolaryngol. 108: 274–283.

Holmström, M., B. Rynnel-Dagöö and B. Wilhelmsson. 1989b. Antibody production in rats after long-term exposure to formaldehyde. Toxicol. Appl. Pharmacol. 100: 328–333.

Holmström, M., B. Wilhelmsson, H. Hellquist and G. Rosén. 1989c. Histological changes in the nasal mucosa in persons occupationally exposed to formaldehyde alone and in combination with wood dust. Acta Otolaryngol. 107: 120–129.

Holness, D.L. and J.R. Nethercott. 1989. Health status of funeral service workers exposed to formaldehyde. Arch. Environ. Health 44: 222–228.

Horton, A.W., R. Tye and K.L. Stemmer. 1963. Experimental carcinogenesis of the lung. Inhalation of gaseous formaldehyde or an aerosol of coal tar by C3H mice. J. Natl. Cancer Inst. 30: 31–43.

Horvath, E.P., Jr., H. Anderson, Jr., W.E. Pierce, L. Hanrahan and J.D. Wendlick. 1988. Effects of formaldehyde on the mucous membranes and lungs. A study of an industrial population. J. Am. Med. Assoc. 259: 701–707.

Hose, J.E. and D.V. Lightner. 1980. Absence of formaldehyde residues in penaeid shrimp exposed to formalin. Aquaculture 21(2): 197–202.

Howard, P.H. 1989. Handbook of environmental fate and exposure data for organic chemicals. Vol. 1. Large production and priority pollutants. Lewis Publishers, Chelsea, Michigan. pp. 101–106.

Howard, P.H., R.S. Boethling, W.F. Jarvis, W.M. Meylan and E.M. Michalenko. 1991. Handbook of environmental degradation rates. Lewis Publishers, Chelsea, Michigan.

Howe, R.B. and K.S. Crump. 1982. GLOBAL82: A computer program to extrapolate quantal animal toxicity data to low doses. Science Research Systems, Ruston, Louisiana.

HSDB (Hazardous Substances Data Bank). 1999. U.S. National Library of Medicine, National Toxicology Information Program, Bethesda, Maryland. March 3, 1999.

Huck, P.M., W.B. Anderson, S.M. Rowley and S.A. Daignault. 1990. Formation and removal of selected aldehydes in a biological drinking-water treatment process. J. Water SRT – Aqua 39(5): 321–333.

IARC (International Agency for Research on Cancer). 1981. Wood, leather and some associated industries. IARC Monogr. Eval. Carcinog. Risk Chem. Hum. 25: 1–412.

IARC (International Agency for Research on Cancer). 1995. Wood dust and formaldehyde. IARC Monogr. Eval. Carcinog. Risks Hum. 62: 217–375.

ICRP (International Commission on Radiological Protection). 1994. Human respiratory tract model for radiological protection. Ann. ICRP 24(1–3) (ICRP Publication 66).

Iversen, O.H. 1988. Formaldehyde and skin tumorigenesis in Sencar mice. Environ. Int. 14: 23–27 [cited in WHO, 1989].

Jakab, G.J. 1992. Relationship between carbon black particulate-bound formaldehyde, pulmonary antibacterial defenses, and alveolar macrophage phagocytosis. Inhal. Toxicol. 4: 325–342.

Jass, H.E. 1985. History and status of formaldehyde in the cosmetics industry. *In*: V. Turoski (ed.), Formaldehyde — analytical chemistry and toxicology. American Chemical Society, Washington, D.C. pp. 229–236 (Advances in Chemistry Series 210).

Jermini, C., A. Weber and E. Grandjean. 1976. [Quantitative determination of various gas-phase components of the side-stream smoke of cigarettes in the room air as a contribution to the problem of passive smoking.] Int. Arch. Occup. Environ. Health 36: 169–181 (in German).

Johannsen, F.R., G.J. Levinskas and A.S. Tegeris. 1986. Effects of formaldehyde in the rat and dog following oral exposure. Toxicol. Lett. 30: 1–6.

Johansson, E.B. and H. Tjälve. 1978. Distribution of [^{14}C]dimethylnitrosoamine in mice. Autoradiographic studies in mice with inhibited and noninhibited dimethylnitrosoamine metabolism and comparison with the distribution of [^{14}C]formaldehyde. Toxicol. Appl. Pharmacol. 45: 565–575.

John, E.M., D.A. Savitz and C.M. Shy. 1994. Spontaneous abortions among cosmetologists. Epidemiology 5: 147–155.

Kamata, E. 1966. Aldehydes in lake and seawater. Bull. Chem. Soc. Jpn. 36: 1227.

Kamata, E., M. Nakadate, O. Uchida, Y. Ogawa, S. Suzuki, T. Kaneko, M. Saito and Y. Kurokawa. 1997. Results of a 28-month chronic inhalation toxicity study of formaldehyde in male Fischer-344 rats. J. Toxicol. Sci. 22: 239–254.

Kaminski, J., A.S. Atwal and S. Mahadevan. 1993. Determination of formaldehyde in fresh and retail milk by liquid column chromatography. J. Assoc. Off. Anal. Chem. Int. 76(5): 1010–1013.

Kao, A.S. 1994. Formation and removal reactions of hazardous air pollutants. J. Air Waste Manage. Assoc. 44: 683–696.

Karickhoff, S.W., D.S. Brown and T.A. Scott. 1979. Sorption of hydrophobic pollutants on natural sediments. Water Res. 13: 241–248.

Keefer, L.K., A.J. Streeter, L.Y. Leung, W.C. Perry, H.S.-W. Hu and T.A. Baillie. 1987. Pharmacokinetic and deuterium isotope effect studies on the metabolism of formaldehyde and formate to carbon dioxide in rats *in vivo*. Drug Metab. Dispos. 15: 300–304.

Kelly, T.J., D.L. Smith and J. Satola. 1999. Emission rates of formaldehyde from materials and consumer products found in California homes. Environ. Sci. Technol. 33(1): 81–88.

Kenaga, E.E. 1980. Predicted bioconcentration factors and soil sorption coefficients of pesticides and other chemicals. Ecotoxicol. Environ. Saf. 4: 26–38.

Kenaga, E.E. and C.A.I. Goring. 1980. Relationship between water solubility, soil sorption, octanol–water partitioning, and concentration of chemicals in biota. *In*: J.G. Eaton, P.R. Parish and A.C. Hendricks (eds.), Aquatic toxicology. American Society for Testing and Materials, Philadelphia, Pennsylvania. pp. 78–115 (ASTM Special Technical Publication 707).

Kepler, G.M., R.B. Richardson, K.T. Morgan and J.S. Kimbell. 1998. Computer simulation of inspiratory nasal airflow and inhaled gas uptake in a rhesus monkey. Toxicol. Appl. Pharmacol. 150: 1–11.

Kerns, W.D., K.L. Pavkov, D.J. Donofrio, E.J. Gralla and J.A. Swenberg. 1983. Carcinogenicity of formaldehyde in rats and mice after long-term inhalation exposure. Cancer Res. 43: 4382–4392.

Kieber, R.J., X. Zhou and K. Mopper. 1990. Formation of carbonyl compounds from UV-induced photodegradation of humic substances in natural waters: Fate of riverine carbon in the sea. Limnol. Oceanogr. 35(7): 1503–1515.

Kilburn, K.H. 1994. Neurobehavioral impairment and seizures from formaldehyde. Arch. Environ. Health 49: 37–44.

Kilburn, K.H. and R.H. Warshaw. 1992. Neurobehavioral effects of formaldehyde and solvents on histology technicians: repeated testing across time. Environ. Res. 58: 134–146.

Kilburn, K.H., R. Warshaw, C.T. Boylen, S.-J.S. Johnson, B. Seidman, R. Sinclair and T. Takaro, Jr. 1985a. Pulmonary and neurobehavioral effects of formaldehyde exposure. Arch. Environ. Health 40: 254–260.

Kilburn, K.H., B.C. Seidman and R. Warshaw. 1985b. Neurobehavioral and respiratory symptoms of formaldehyde and xylene exposure in histology technicians. Arch. Environ. Health 40: 229–233.

Kilburn, K.H., R. Warshaw and J.C. Thornton. 1987. Formaldehyde impairs memory, equilibrium, and dexterity in histology technicians: effects which persist for days after exposure. Arch. Environ. Health 42: 117–120.

Kilburn, K.H., R. Warshaw, J.C. Thornton and I. Husmark. 1989. An examination of factors that could affect choice reaction time in histology technicians. Am. J. Ind. Med. 15: 679–686.

Kimbell, J.S., M.N. Godo, E.A. Gross, D.R. Joyner, R.B. Richardson and K.T. Morgan. 1997. Computer simulation of inspiratory airflow in all regions of the F344 rat nasal passages. Toxicol. Appl. Pharmacol. 145: 388–398.

Kitaeva, L.V., E.M. Kitaeva and M.N. Pimenova. 1990. [Cytopathic and cytogenetic effects of chronic inhalation of formaldehyde on the female rat's germ and marrow cells.] Tsitologiya 32: 1212–1216 (in Russian).

Kitaeva, L.V., E.A. Mikheeva, L.F. Shelomova and P.Ya. Shvartsman. 1996. [Genotoxic effect of formaldehyde in somatic human cells *in vivo*.] Genetika 32: 1287–1290 (in Russian).

Kitchens, J.F., R.E. Casner, G.S. Edwards, W.E. Harward and B.J. Macri. 1976. Investigation of selected potential environmental contaminants: formaldehyde. U.S. Environmental Protection Agency, Washington, D.C. 204 pp. (EPA 560/2-76-009).

Kligerman, A.D., M.C. Phelps and G.L. Erexson. 1984. Cytogenetic analysis of lymphocytes from rats following formaldehyde inhalation. Toxicol. Lett. 21: 241–246.

Klus, H. and H. Kuhn. 1982. [Distribution of different components of tobacco smoke between main-current and side-current smoke.] Beitr. Tabakforsch. Int. 11: 229–265 (in German).

Kochhar, R., V. Nanda, B. Nagi and S.K. Mehta. 1986. Formaldehyde-induced corrosive gastric cicatrization: case report. Hum. Toxicol. 5: 381–382.

Krasner, S.W., M.J. McGuire, J.G. Jacangelo, N.L. Patania, K.M. Reagan and E.M. Aieta. 1989. The occurrence of disinfection by-products in US drinking water. J. Am. Water Works Assoc. 81(8): 41–53.

Krivanek, N.D., J.W. McAlack and N.C. Chromey. 1983. Mouse skin painting-initiation-promotion study with formaldehyde solutions — preliminary results. Toxicologist 3: 144 [cited in WHO, 1989].

Kroschwitz, J.I. (ed.). 1991. Kirk-Othmer encyclopedia of chemical technology. 4th edition. Vol. 11. John Wiley and Sons, New York, N.Y.

Krzyzanowski, M., J.J. Quackenboss and M.D. Lebowitz. 1990. Chronic respiratory effects of indoor formaldehyde exposure. Environ. Res. 52: 117–125.

Kulle, T.J. 1993. Acute odor and irritation response in healthy nonsmokers with formaldehyde exposure. Inhal. Toxicol. 5: 323–332.

Lawrence, J.F. and J.R. Iyengar. 1983. The determination of formaldehyde in beer and soft drinks by HPLC of the 2,4-dinitrophenylhydrazone derivative. Int. J. Environ. Anal. Chem. 15: 47–52.

Liber, H.L., K. Benforado, R.M. Crosby, D. Simpson and T.R. Skopek. 1989. Formaldehyde-induced and spontaneous alterations in human *hprt* DNA sequence and mRNA expression. Mutat. Res. 226: 31–37.

Lindbohm, M.-L., K. Hemminki, M.G. Bonhomme, A. Anttila, K. Rantala, P. Heikkilä and M.J. Rosenberg. 1991. Effects of paternal occupational exposure on spontaneous abortions. Am. J. Public Health 81: 1029–1033.

Lipari, F., J.M. Dasch and W.F. Scruggs. 1984. Aldehyde emissions from wood-burning fireplaces. Environ. Sci. Technol. 18: 326–330.

Little, J.C., A.T. Hodgson and A.J. Gadgil. 1994. Modeling emissions of volatile organic compounds from new carpets. Atmos. Environ. 28(2): 227–234.

Lockhart, C.L. 1972. Control of nematodes in peat with formaldehyde. Can. Plant Dis. Surv. 52: 104.

Lowe, D.C. and U. Schmidt. 1983. Formaldehyde measurements in the nonurban atmosphere. J. Geophys. Res. 88: 10 844–10 858.

Lowe, D.C., U. Schmidt and D.H. Ehhalt. 1980. A new technique for measuring tropospheric formaldehyde. Geophys. Res. Lett. 7: 825–828.

Luce, D., M. Gérin, A. Leclerc, J.-F. Morcet, J. Brugère and M. Goldberg. 1993. Sinonasal cancer and occupational exposure to formaldehyde and other substances. Int. J. Cancer 53: 224–231.

Mackay, D. 1991. Multimedia environmental models: the fugacity approach. Lewis Publishers, Chelsea, Michigan.

Mackay, D. and S. Paterson. 1991. Evaluating the multimedia fate of organic chemicals: a Level III fugacity model. Environ. Sci. Technol. 25: 427–436.

Mackay, D., W.-Y. Shiu and K.-C. Ma. 1995. Illustrated handbook of physical-chemical properties and environmental fate of organic compounds. Vol. IV. Lewis Publishers, Chelsea, Michigan.

Malaka, T. and A.M. Kodama. 1990. Respiratory health of plywood workers occupationally exposed to formaldehyde. Arch. Environ. Health 45: 288–294.

Marsh, G.M., R.A. Stone and V.L. Henderson. 1992. Lung cancer mortality among industrial workers exposed to formaldehyde: a Poisson regression analysis of the National Cancer Institute study. Am. Ind. Hyg. Assoc. J. 53: 681–691.

Marsh, G.M., R.A. Stone, N.A. Esmen, V.L. Henderson and K. Lee. 1996. Mortality among chemical workers in a factory where formaldehyde was used. Occup. Environ. Med. 53: 613–627.

Martin, W.J. 1990. A teratology study of inhaled formaldehyde in the rat. Reprod. Toxicol. 4: 237–239.

Masaru, N., F. Syozo and K. Saburo. 1976. Effects of exposure to various injurious gases on germination of lily pollen. Environ. Pollut. 11: 181–188.

Matanoski, G.M. 1989. Risks of pathologists exposed to formaldehyde. National Institute for Occupational Safety and Health, Cincinnati, Ohio. 45 pp. (PB91-173682).

Maurice, F., J.-P. Rivory, P.H. Larsson, S.G.O. Johansson and J. Bousquet. 1986. Anaphylactic shock caused by formaldehyde in a patient undergoing long-term hemodialysis. J. Allergy Clin. Immunol. 77: 594–597.

McCrillis, R.C., E.M. Howard, Z. Guo, K.A. Krebs, R. Fortmann and H.-C. Lao. 1999. Characterization of curing emissions from conversion varnishes. J. Air Waste Manage. Assoc. 49: 70–75.

McDonald, A. 1996. Letter dated April 30, 1996, from LEVER, a division of UL Canada, Inc., Toronto, Ontario, to J. Sealy, Priority Substances Section, Bureau of Chemical Hazards, Health Canada, Ottawa, Ontario, regarding levels of PSL2 substances in Canadian consumer products.

McMartin, K.E., G. Martin-Amat, P.E. Noker and T.R. Tephly. 1979. Lack of a role for formaldehyde in methanol poisoning in the monkey. Biochem. Pharmacol. 28: 645–649.

Meek, M.E., A. Atkinson and J. Sitwell. 1985. Background paper on formaldehyde prepared for WHO working group on indoor air quality: radon and formaldehyde. Bureau of Chemical Hazards, Health Protection Branch, Health and Welfare Canada, Ottawa, Ontario. pp. 1–124.

Meek, M.E., R. Newhook, R. Liteplo and V. Armstrong. 1994. Approach to assessment of risk to human health for Priority Substances under the *Canadian Environmental Protection Act*. J. Environ. Sci. Health C12: 105–134.

Merletti, F., P. Boffetta, G. Ferro, P. Pisani and B. Terracini. 1991. Occupation and cancer of the oral cavity or oropharynx in Turin, Italy. Scand. J. Work Environ. Health 17: 248–254.

Meyer, B. and K. Hermanns. 1985. Formaldehyde release from pressed wood products. *In*: V. Turoski (ed.), Formaldehyde — analytical chemistry and toxicology. American Chemical Society, Washington, D.C. pp. 101–116 (Advances in Chemistry Series 210).

Migliore, L., L. Ventura, R. Barale, N. Loprieno, S. Castellino and R. Pulci. 1989. Micronuclei and nuclear anomalies induced in the gastrointestinal epithelium of rats treated with formaldehyde. Mutagenesis 4: 327–334.

Ministers' Expert Advisory Panel. 1995. Report of the Ministers' Expert Advisory Panel on the second Priority Substances List, under the *Canadian Environmental Protection Act* (CEPA). Government of Canada, Ottawa, Ontario. 26 pp.

Miyake, T. and T. Shibamoto. 1995. Quantitative analysis by gas chromatography of volatile carbonyl compounds in cigarette smoke. J. Chromatogr. A 693: 376–381.

Möhler, K. and G. Denbsky. 1970. [Determination of formaldehyde in foods.] Z. Lebensm.-Unters. Forsch. 142: 109 (in German) [cited in WHO, 1989, but not listed among references; cited in Owen *et al.*, 1990, as "Mohler, K. and Denby, G. (1970), as reported in Cantoni *et al.* (1987)."]

Monteiro-Riviere, N.A. and J.A. Popp. 1986. Ultrastructural evaluation of acute nasal toxicity in the rat respiratory epithelium in response to formaldehyde gas. Fundam. Appl. Toxicol. 6: 251–262.

Monticello, T.M. and K.T. Morgan. 1994. Cell proliferation and formaldehyde-induced respiratory carcinogenesis. Risk Anal. 14: 313–319.

Monticello, T.M., K.T. Morgan, J.I. Everitt and J.A. Popp. 1989. Effects of formaldehyde gas on the respiratory tract of rhesus monkeys. Pathology and cell proliferation. Am. J. Pathol. 134: 515–527.

Monticello, T.M., F.J. Miller and K.T. Morgan. 1991. Regional increases in rat nasal epithelial cell proliferation following acute and subchronic inhalation of formaldehyde. Toxicol. Appl. Pharmacol. 111: 409–421.

Monticello, T.M., J.A. Swenberg, E.A. Gross, J.R. Leininger, J.S. Kimbell, S. Seilkop, T.B. Starr, J.E. Gibson and K.T. Morgan. 1996. Correlation of regional and nonlinear formaldehyde-induced nasal cancer with proliferating populations of cells. Cancer Res. 56: 1012–1022.

Moore, G. 2000. Personal communication to R. Beauchamp, Priority Substances Section, Health Canada, Ottawa, Ontario, regarding formaldehyde in pest control products. E-mail dated March 28, 2000, from Pest Management Regulatory Agency, Ottawa, Ontario.

Morgan, K.T., D.L. Patterson and E.A. Gross. 1986a. Responses of the nasal mucociliary apparatus of F-344 rats to formaldehyde gas. Toxicol. Appl. Pharmacol. 82: 1–13.

Morgan, K.T., E.A. Gross and D.L. Patterson. 1986b. Distribution, progression, and recovery of acute formaldehyde-induced inhibition of nasal mucociliary function in F-344 rats. Toxicol. Appl. Pharmacol. 86: 448–456.

Morgan, K.T., X.-Z. Jiang, T.B. Starr and W.D. Kerns. 1986c. More precise localization of nasal tumors associated with chronic exposure of F-344 rats to formaldehyde gas. Toxicol. Appl. Pharmacol. 82: 264–271.

Mutters, R.G., M. Madore and A. Bytnerowicz. 1993. Formaldehyde exposure affects growth and metabolism of common bean. Air Waste 43: 113–116.

Natarajan, A.T., F. Darroudi, C.J.M. Bussman and A.C. van Kesteren-van Leeuwen. 1983. Evaluation of the mutagenicity of formaldehyde in mammalian cytogenetic assays *in vivo* and *vitro*. Mutat. Res. 122: 355–360.

NATES (National Analysis of Trends in Emergencies System). 1996. NATES database. Environmental Emergencies Branch, Environment Canada, Hull, Quebec.

NCASI (National Council of the Paper Industry for Air and Stream Improvement). 1994. Evaluation of methods to estimate releasable formaldehyde from formaldehyde resin containing wood and paper product dusts (Technical Bulletin for NCASI No. 664).

Nishi, K., M. Yamada and C. Wakasugi. 1988. Formaldehyde poisoning: report of an autopsy case. Jpn. J. Leg. Med. 42: 85–89.

Norton, L.A. 1991. Common and uncommon reactions to formaldehyde-containing nail hardeners. Semin. Dermatol. 10: 29–33.

Novamann International. 1997. SWARU incinerator emission characterization for compliance with certificate of approval. Prepared by Novamann (Ontario) Inc. for Regional Municipality of Hamilton-Wentworth and Laidlaw Technologies, Mississauga, Ontario.

NRC (National Research Council). 1981. Formaldehyde and other aldehydes. National Academy Press, Washington, D.C. 340 pp.

NRC (National Research Council). 1982. Formaldehyde and other aldehydes. U.S. Environmental Protection Agency, Washington, D.C. (EPA-600/6-82-002).

Nuccio, J., P.J. Seaton and R.J. Kieber. 1995. Biological production of formaldehyde in the marine environment. Limnol. Oceanogr. 40(3): 521–527.

Nunn, A.J., A.A. Craigen, J.H. Darbyshire, K.M. Venables and A.J. Newman Taylor. 1990. Six year follow up of lung function in men occupationally exposed to formaldehyde. Br. J. Ind. Med. 47: 747–752.

O'Connor, B. and R. Voss. 1997. Guidance with respect to PSL2 survey. Pulp and Paper Research Institute of Canada, Pointe-Claire, Quebec. April 2, 1997.

Olin, K.L., G.N. Cherr, E. Rifkin and C.L. Keen. 1996. The effects of some redox-active metals and reactive aldehydes on DNA–protein cross-links *in vitro*. Toxicology 110: 1–8.

Olsen, J.H. and S. Asnaes. 1986. Formaldehyde and the risk of squamous cell carcinoma of the sinonasal cavities. Br. J. Ind. Med. 43: 769–774.

Owen, B.A., C.S. Dudney, E.L. Tan and C.E. Easterly. 1990. Formaldehyde in drinking water: Comparative hazard evaluation and an approach to regulation. Regul. Toxicol. Pharmacol. 11: 200–236.

Paraskevopoulos, G., S.L. Singleton and R. McLaren. 1995. Hydrocarbon reactivity scales: a critical review. Institute for Environmental Research and Technology, National Research Council, Ottawa, Ontario (Report No. ER-1344-955).

Partanen, T. 1993. Formaldehyde exposure and respiratory cancer — a meta-analysis of the epidemiologic evidence. Scand. J. Work Environ. Health 19: 8–15.

Partanen, T., T. Kauppinen, S. Hernberg, J. Nickels, R. Luukkonen, T. Hakulinen and E. Pukkala. 1990. Formaldehyde exposure and respiratory cancer among woodworkers — an update. Scand. J. Work Environ. Health 16: 394–400.

Patterson, D.L., E.A. Gross, M.S. Bogdanffy and K.T. Morgan. 1986. Retention of formaldehyde gas by the nasal passages of F-344 rats. Toxicologist 6: 55.

Pazdrak, K., P. Górski, A. Krakowiak and U. Ruta. 1993. Changes in nasal lavage fluid due to formaldehyde inhalation. Int. Arch. Occup. Environ. Health 64: 515–519.

Perry, R.H. and D. Green. 1984. Perry's chemical handbook of physical and chemical data. 6th edition. McGraw-Hill, New York, N.Y.

Persson, L. 1973. Studies on the influence of lime, formalin, formic acid and ammonium persulphate on the eggs and larvae of *Ostertagia ostertagi* and *Cooperia oncophora* in liquid cattle manure. Zentralbl. Veterenaermed. 20: 729–740.

Piersol, P. 1995. Build Green and conventional materials off-gassing tests. Prepared by ORTECH Corporation for Canada Mortgage and Housing Corporation. February 6, 1995. 24 pp. (Report No. 94-G53-B0106).

Piletta-Zanin, P.A., F. Pasche-Koo, P.C. Auderset, D. Huggenberger, J.-H. Saurat and C. Hauser. 1996. Detection of formaldehyde in ten brands of moist baby toilet tissue by the acetylacetone methods and high-performance liquid chromatography. Dermatology 193: 170.

Pottern, L.M., E.F. Heineman, J.H. Olsen, E. Raffn and A. Blair. 1992. Multiple myeloma among Danish women: employment history and workplace exposures. Cancer Causes Control 3: 427–432.

Preuss, P.W., R.L. Dailey and E.S. Lehman. 1985. Exposure to formaldehyde. *In*: V. Turoski (ed.), Formaldehyde — analytical chemistry and toxicology. American Chemical Society, Washington, D.C. pp. 247–259 (Advances in Chemistry Series 210).

Priha, E. 1995. Are textile formaldehyde regulations reasonable? Experiences from the Finnish textile and clothing industries. Regul. Toxicol. Pharmacol. 22: 243–249.

Ramanathan, V., R.J. Cicerone, H.B. Singh and J.T. Kiehl. 1985. Trace gas trends and their potential role in climate change. J. Geophys. Res. 90: 5547–5566.

Ramdahl, T., I. Alfheim, S. Rustad and T. Olsen. 1982. Chemical and biological characterization of emissions from small residential stove burning wood and charcoal. Chemosphere 11(4): 601–611.

Reardon, I.S. and R.M. Harrell. 1990. Acute toxicity of formalin and copper sulfate to striped bass fingerlings held in varying salinities. Aquaculture 87(3/4): 255–270.

Recio, L., S. Sisk, L. Pluta, E. Bermudez, E.A. Gross, Z. Chen, K. Morgan and C. Walker. 1992. *p53* mutations in formaldehyde-induced nasal squamous cell carcinomas in rats. Cancer Res. 52: 6113–6116.

Rehbein, H. 1986. [Formation of formaldehyde in fish products.] Lebensm.-Chem. Gerichtl. Chem. 40: 147–118 (in German) [cited in WHO, 1989].

Reinhardt, T.E. 1991. Monitoring firefighter exposure to air toxins at prescribed burns of forest and range biomass. Pacific Northwest Research Station, Forest Service, U.S. Department of Agriculture, Portland, Oregon. 8 pp. (Research Paper PNW-RP-441).

Restani, P., A.R. Restelli and C.L. Galli. 1992. Formaldehyde and hexamethylenetetramine as food additives: chemical interactions and toxicology. Food Addit. Contam. 9(5): 597–605.

Reuzel, P.G.J., J.W.G.M. Wilmer, R.A. Woutersen, A. Zwart, P.J.A. Rombout and V.J. Feron. 1990. Interactive effects of ozone and formaldehyde on the nasal respiratory lining epithelium in rats. J. Toxicol. Environ. Health 29: 279–292.

Richardson, A. 1999. Personal communication from the Cosmetic Program, Product Safety Bureau, Health Canada, to R. Beauchamp, Priority Substances Section, Bureau of Chemical Hazards, Health Canada, Ottawa, Ontario, dated December 15, 1999, regarding formaldehyde in cosmetics.

Riedel, F., E. Hasenauer, P.J. Barth, A. Koziorowski and C.H.L. Rieger. 1996. Formaldehyde exposure enhances inhalative allergic sensitization in the guinea pig. Allergy 51: 94–96.

Rietbrock, N. 1969. [Kinetics and pathways of methanol metabolism in rats.] Exp. Pathol. Pharmacol. 263: 88–105 (in German) [cited in IPCS, 1989].

Ritchie, I.M. and R.G. Lehnen. 1987. Formaldehyde-related health complaints of residents living in mobile and conventional homes. Am. J. Public Health 77: 323–328.

RIVM (National Institute of Public Health and the Environment). 1992. Exploratory report for formaldehyde. Bilthoven, Netherlands (Report No. 710401018).

Rose, D. 1998. Personal communication. Calculation of total acrolein emissions from coal-based plants and total aldehyde emissions from coal-based and oil-based plants in Canada. Oil, Gas and Energy Division, Air Pollution Prevention Directorate, Environment Canada.

Ross, J.S., J.G. Rycroft and E. Cronin. 1992. Melamine-formaldehyde contact dermatitis in orthopaedic practice. Contact Dermatitis 26: 203–204.

Roush, G.C., J. Walrath, L.T. Stayner, S.A. Kaplan, J.T. Flannery and A. Blair. 1987. Nasopharyngeal cancer, sinonasal cancer, and occupations related to formaldehyde: A case–control study. J. Natl. Cancer Inst. 79: 1221–1224.

Rusch, G.M., H.F. Bolte and W.E. Rinehart. 1983. A 26-week inhalation toxicity study with formaldehyde in the monkey, rat and hamster. *In*: J.E. Gibson (ed.), Formaldehyde toxicity. Hemisphere Publishing, Washington, D.C. pp. 98–110.

Saillenfait, A.M., P. Bonnet and J. de Ceaurriz. 1989. The effects of maternally inhaled formaldehyde on embryonal and foetal development in rats. Food Chem. Toxicol. 8: 545–548.

Saladino, A.J., J.C. Willey, J.F. Lechner, R.C. Grafstrom, M. LaVeck and C.C. Harris. 1985. Effects of formaldehyde, acetaldehyde, benzoyl peroxide, and hydrogen peroxide on cultured normal human bronchial epithelial cells. Cancer Res. 45: 2522–2526.

Sangster, J. 1989. Octanol–water partition coefficients of simple organic compounds. J. Phys. Chem. Ref. Data 18: 1111–1230.

Satsumabayashi, H., H. Kurita, Y.S. Chang, G.R. Carmichael and H. Ueda. 1995. Photochemical formations of lower aldehydes and lower fatty acids under long-range transport in central Japan. Atmos. Environ. 29(2): 255–266.

Sauder, L.R., M.D. Chatham, D.J. Green and T.J. Kulle. 1986. Acute pulmonary response to formaldehyde exposure in healthy nonsmokers. J. Occup. Med. 28: 420–424.

Sauder, L.R., D.J. Green, M.D. Chatham and T.J. Kulle. 1987. Acute pulmonary response of asthmatics to 3.0 ppm formaldehyde. Toxicol. Ind. Health 3: 569–578.

Schachter, E.N., T.J. Witek, Jr., T. Tosun, B.P. Leaderer and G.J. Beck. 1986. A study of respiratory effects from exposure to 2 ppm formaldehyde in healthy subjects. Arch. Environ. Health 41: 229–239.

Schachter, E.N., T.J. Witek, Jr., D.J. Brody, T. Tosun, G.J. Beck and B.P. Leaderer. 1987. A study of respiratory effects from exposure to 2.0 ppm formaldehyde in occupationally exposed workers. Environ. Res. 44: 188–205.

Schauer, J.J., M.L. Kleeman, G.R. Cass and B.R.T. Simoneit. 1999. Measurement of emissions from air pollution sources. 1. C_1 through C_{29} organic compounds from meat charbroiling. Environ. Sci. Technol. 33: 1566–1577.

Scheman, A.J., P.A. Carrol, K.H. Brown and A.H. Osburn. 1998. Formaldehyde-related textile allergy: an update. Contact Dermatitis 38: 332–336.

Scheuplein, R.J. 1985. Formaldehyde: The Food and Drug Administration's perspective. *In*: V. Turoski (ed.), Formaldehyde — analytical chemistry and toxicology. American Chemical Society, Washington, D.C. pp. 237–245 (Advances in Chemistry Series 210).

Schlitt, H. and H. Knöppel. 1989. Carbonyl compounds in mainstream and sidestream cigarette smoke. *In*: C. Bieva, Y. Courtois and M. Govaerts (eds.), Present and future of indoor air quality. Excerpta Medica, Amsterdam. pp. 197–206.

Schriever, E., R. Marutzky and D. Merkel. 1983. [Examination of emissions from small wood-fired combustion furnaces.] Staub-Reinhalt. Luft 43: 62–65 (in German).

SEAM Database. 1996. Information from SEAM (Surface, Environment, and Mining) Database provided to J. Sealy, Environmental Health Centre, Health Canada, by M.J. Pak, Lab and Systems Management, B.C. Ministry of Environment, Lands and Parks.

Seidenberg, J.M. and R.A. Becker. 1987. A summary of the results of 55 chemicals screened for developmental toxicity in mice. Teratogen. Carcinogen. Mutagen. 7: 17–28.

Sellakumar, A.R., C.A. Snyder, J.J. Solomon and R.E. Albert. 1985. Carcinogenicity of formaldehyde and hydrogen chloride in rats. Toxicol. Appl. Pharmacol. 81: 401–406.

Skov, H., J. Hjorth, C. Lohse, N.R. Jensen and G. Restelli. 1992. Products and mechanisms of the reactions of the nitrate radical (NO_3) with isoprene, 1,3-butadiene and 2,3-dimethyl-1,3-butadiene in air. Atmos. Environ. 26A(15): 2771–2783.

Smith, J. 2000. Personal communication. Pest Management Regulatory Agency, Health Canada.

Snyder, R.D. and B. van Houten. 1986. Genotoxicity of formaldehyde and an evaluation of its effects on the DNA repair process in human diploid fibroblasts. Mutat. Res. 165: 21–30.

Soffritti, M., C. Maltoni, F. Maffei and R. Biagi. 1989. Formaldehyde: an experimental multipotential carcinogen. Toxicol. Ind. Health 5: 699–730.

Sotelo, C.G., C. Piñeiro and R.I. Pérez-Martín. 1995. Denaturation of fish protein during frozen storage: role of formaldehyde. Z. Lebensm.-Unters. Forsch. 200: 14–23.

Staudinger, J. and P.V. Roberts. 1996. A critical review of Henry's law constants for environmental applications. Crit. Rev. Environ. Sci. Technol. 26: 205–297.

Stayner, L.T., L. Elliott, L. Blade, R. Keenlyside and W. Halperin. 1988. A retrospective cohort mortality study of workers exposed to formaldehyde in the garment industry. Am. J. Ind. Med. 13: 667–681.

Stenton, S.C. and D.J. Hendrick. 1994. Formaldehyde. Immunol. Allergy Clin. North Am. 14: 635–657.

Sterling, T.D. and J.J. Weinkam. 1994. Mortality from respiratory cancers (including lung cancer) among workers employed in formaldehyde industries. Am. J. Ind. Med. 25: 593–602.

Stills, J.B. and J.L. Allen. 1979. Residues of formaldehyde undetected in fish exposed to formalin. Prog. Fish Cult. 41(2): 67–68.

Stroup, N.E., A. Blair and G.E. Erikson. 1986. Brain cancer and other causes of death in anatomists. J. Natl. Cancer Inst. 77: 1217–1224.

Subramaniam, R.P., R.B. Richardson, K.T. Morgan, R.A. Guilmette and J.S. Kimbell. 1998. Computational fluid dynamics simulations of inspiratory airflow in the human nose and nasopharynx. Inhal. Toxicol. 10: 92–120.

Suruda, A., P. Schulte, M. Boeniger, R.B. Hayes, G.K. Livingston, K. Steenland, P. Stewart, R. Herrick, D. Douthit and M.A. Fingerhut. 1993. Cytogenetic effects of formaldehyde exposure in students of mortuary science. Cancer Epidemiol. Biomarkers Prev. 2: 453–460.

Suskov, I.I. and L.A. Sazonova. 1982. Cytogenetic effects of epoxy, phenol-formaldehyde and polyvinylchloride resins in man. Mutat. Res. 104: 137–140.

Sverdrup, G.M., K.B. Riggs, T.J. Kelly, R.E. Barrett, R.G. Peltier and J.A. Cooper. 1994. Toxic emissions from a cyclone burner boiler with an ESP and with the SNOX demonstration and from a pulverized coal burner boiler with an ESP/wet flue gas desulfurization system. Presented at the 87th Annual Meeting and Exhibition of the Air and Waste Management Association, Cincinnati, Ohio, June 19–24, 1994 (94-WA73.02).

Swenberg, J.A., W.D Kerns, R.I. Mitchell, E.J. Gralla and K.L. Pavkov. 1980. Induction of squamous cell carcinomas of the rat nasal cavity by inhalation exposure to formaldehyde vapor. Cancer Res. 40: 3398–3402.

Swenberg, J.A., E.A. Gross, J. Martin and J.A. Popp. 1983. Mechanisms of formaldehyde toxicity. *In*: J.E. Gibson (ed.), Formaldehyde toxicity. Hemisphere Publishing, Washington, D.C. pp. 132–147.

Swenberg, J.A., E.A. Gross, J. Martin and H.A. Randall. 1986. Localization and quantitation of cell proliferation following exposure to nasal irritants. *In*: C.S. Barrow (ed.), Toxicology of the nasal passages. Hemisphere Publishing, Washington, D.C. pp. 291–300.

Tabor, R.G. 1988. Control of formaldehyde release from wood products adhesives. Comments Toxicol. 2(3): 191–200.

Takahashi, M., R. Hasegawa, F. Furukawa, K. Toyoda, H. Sato and Y. Hayashi. 1986. Effects of ethanol, potassium metabisulfite, formaldehyde and hydrogen peroxide on gastric carcinogenesis in rats after initiation with N-methyl-N'-nitro-N-nitrosoguanidine. Jpn. J. Cancer Res. 77: 118–124.

Tanner, R.L., B. Zielinska, E. Ueberna and G. Harshfield. 1994. Measurements of carbonyls and the carbon isotopy of formaldehyde at a coastal site in Nova Scotia during NARE. Final report. Prepared by Desert Research Institute, Reno, Nevada, for the Office of Global Programs, National Oceanic and Atmospheric Administration, Silver Spring, Maryland. 25 pp. (DRI Document 3910-IFI).

Tardif, P.R. 1998. Personal communication. Letter with attachments dated March 18, 1998, to E. Easson, Bureau of Chemical Hazards, Health Canada, Ottawa, Ontario, regarding formaldehyde emission information from particleboard and medium-density fibreboard. Canadian Technical Affairs, Composite Panel Association, Westmount, Quebec.

Tarkowski, M. and P. Gorski. 1995. Increased IgE antiovalbumin level in mice exposed to formaldehyde. Int. Arch. Allergy Immunol. 106: 422–424.

Tashkov, W. 1996. Determination of formaldehyde in foods, biological media and technological materials by head space gas chromatography. Chromatographia 43(11/12): 625–627.

Taskinen, H., P. Kyyronen, K. Hemminki, M. Hoikkala, K. Lajunen and M.-L. Lindbohm. 1994. Laboratory work and pregnancy outcome. J. Occup. Med. 36: 311–319.

Thomann, R.V. 1989. Bioaccumulation model of organic chemical distribution in aquatic food chains. Environ. Sci. Technol. 23(6): 699–707.

Thomson, E.J., S. Shackleton and J.M. Harrington. 1984. Chromosome aberrations and sister-chromatid exchange frequencies in pathology staff occupationally exposed to formaldehyde. Mutat. Res. 141: 89–93.

Tiemstra, E. 1989. Gas pipeline contaminants. American Gas Association, Washington, D.C. pp. 545–548 (89-DT-84).

Til, H.P., R.A. Woutersen and V.J. Feron. 1988. Evaluation of the oral toxicity of acetaldehyde and formaldehyde in a 4-week drinking water study in rats. Food Chem. Toxicol. 26: 447–452.

Til, H.P., R.A. Woutersen, V.J. Feron, V.H.M. Hollanders and H.E. Falke. 1989. Two-year drinking-water study of formaldehyde in rats. Food Chem. Toxicol. 27: 77–87.

Titenko-Holland, N., A.J. Levine, M.T. Smith, P.J.E. Quintana, M. Boeniger, R. Hayes, A. Suruda and P. Schulte. 1996. Quantification of epithelial cell micronuclei by fluorescence *in situ* hybridization (FISH) in mortuary science students exposed to formaldehyde. Mutat. Res. 371: 237–248.

Tobe, M., T. Kaneko, Y. Uchida, E. Kamata, Y. Ogawa, Y. Ikeda and M. Saito. 1985. Studies on the inhalation toxicity of formaldehyde. Tokyo National Sanitary and Medical Laboratory Service, Toxicity. 43 pp. (TR-85-0236) [cited in WHO, 1989].

Tobe, M., K. Naito and Y. Kurokawa. 1989. Chronic toxicity study on formaldehyde administered orally to rats. Toxicology 56: 79–86.

Tsuchiya, K., Y. Hayashi, M. Onodera and T. Hasegawa. 1975. Toxicity of formaldehyde in experimental animals — concentrations of the chemical in the elution from dishes of formaldehyde resin in some vegetables. Keio J. Med. 24: 19–37.

Tsuchiya, H., S. Ohtani, K. Yamada, M. Akagiri, N. Takagi and M. Sato. 1994. Determination of formaldehyde in reagents and beverages using flow injection. Analyst 119: 1413–1416.

Tsuda, M., N. Frank, S. Sato and T. Sugimura. 1988. Marked increase in the urinary level of N-nitrosothioproline after ingestion of cod with vegetables. Cancer Res. 48: 4049–4052.

Tucker, W.G. 1990. Building with low-emitting materials and products: where do we stand? *In*: Indoor Air '90. The fifth international conference on indoor air quality and climate, Toronto, Ontario, July 29 – August 3, 1990. Vol. 3. pp. 251–256.

Upreti, R.K., M.Y.H. Farooqui, A.E. Ahmed and G.A.S. Ansari. 1987. Toxicokinetics and molecular interaction of [^{14}C]-formaldehyde in rats. Arch. Environ. Contam. Toxicol. 16: 263–273.

Ura, H., P. Nowak, S. Litwin, P. Watts, R.D. Bonfil and A.J. Klein-Szanto. 1989. Effects of formaldehyde on normal xenotransplanted human tracheobronchial epithelium. Am. J. Pathol. 134: 99–106.

U.S. EPA (United States Environmental Protection Agency). 1985. Health and environmental effects profile for formaldehyde. Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment, Office of Research and Development, Cincinnati, Ohio (EPA/600/X-85/362).

U.S. EPA (United States Environmental Protection Agency). 1990. Evaluation of emission factors for formaldehyde from certain wood processing operations. Final report, May–August 1989. Office of Research and Development, Air and Energy Engineering Research Laboratory, Research Triangle Park, North Carolina (EPA/600/8-90/052).

U.S. EPA (United States Environmental Protection Agency). 1993. Motor vehicle-related air toxics study. Office of Mobile Sources, Emission Planning and Strategies Division, Ann Arbor, Michigan. April (EPA 420-R-93-005).

Vargová, M., J. Wagnerová, A. Lisková, J. Jakubovský, M. Gajdová, E. Stolcová, J. Kubová, J. Tulinská and R. Stenclová. 1993. Subacute immunotoxicity study of formaldehyde in male rats. Drug Chem. Toxicol. 16: 255–275.

Vasudeva, N. and C. Anand. 1996. Cytogenetic evaluation of medical students exposed to formaldehyde vapor in the gross anatomy dissection laboratory. J. Am. Coll. Health 44: 177–179.

Vaughan, T.L., C. Strader, S. Davis and J.R. Daling. 1986a. Formaldehyde and cancers of the pharynx, sinus and nasal cavity: I. Occupational exposures. Int. J. Cancer 38: 677–683.

Vaughan, T.L., C. Strader, S. Davis and J.R. Daling. 1986b. Formaldehyde and cancers of the pharynx, sinus and nasal cavity: II. Residential exposures. Int. J. Cancer 38: 685–688.

Veith, G.D., K.J. Macek, S.R. Petrocelli and J. Carroll. 1980. An evaluation of using partition coefficients and water solubility to estimate bioconcentration factors for organic chemicals in fish. *In*: J.G. Eaton, P.R. Parrish and A.C. Hendricks (eds.), Aquatic toxicology. American Society for Testing and Materials, Philadelphia, Pennsylvania. pp. 116–129 (ASTM Special Technical Publication 707).

Verschueren, K. 1983. Handbook of environmental data on organic chemicals. 2nd edition. Van Nostrand Reinhold, New York, N.Y.

Vincenzi, C., L. Guerra, A.M. Peluso and V. Zucchelli. 1992. Allergic contact dermatitis due to phenol-formaldehyde resins in a knee-guard. Contact Dermatitis 27: 54.

Walker, B.L. and C.D. Cooper. 1992. Air pollution emission factors for medical waste incinerators. J. Air Waste Manage. Assoc. 42: 784–791.

Wang, W.C., Y.L. Yung, A.A. Lacis, T. Mo and J.E. Hansen. 1976. Greenhouse effects due to man-made perturbations of trace gases. Science 194: 685–689.

Wantke, F., W. Hemmer, T. Haglmuller, M. Gotz and R. Jarisch. 1995. Anaphylaxis after dental treatment with a formaldehyde-containing tooth filling material. Allergy 50: 274–276.

Warneck, P., W. Klippel and G.K. Moortgat. 1978. [Formaldehyde in tropospheric clean air.] Ber. Bunsenges. Phys. Chem. 82: 1136–1142 (in German).

Weast, R.C. (ed.). 1982–1983. Handbook of chemistry and physics. 62nd edition. CRC Press, Boca Raton, Florida.

Wellborn, T.L. 1969. Toxicity of nine therapeutic and herbicidal compounds to striped bass. Prog. Fish Cult. 31(1): 27–32.

West, S., A. Hildesheim and M. Dosemeci. 1993. Non-viral risk factors for nasopharyngeal carcinoma in the Philippines: Results from a case–control study. Int. J. Cancer 55: 722–727.

WHO (World Health Organization). 1989. Formaldehyde. International Programme on Chemical Safety, Geneva. 219 pp. (Environmental Health Criteria 89).

Wickramaratne, G.A. de S. 1987. The Chernoff-Kavlock assay: its validation and application in rats. Teratogen. Carcinogen. Mutagen. 7: 73–83.

Wilmer, J.W.G.M., R.A. Woutersen, L.M. Appelman, W.R. Leeman and V.J. Feron. 1987. Subacute (4-week) inhalation toxicity study of formaldehyde in male rats: 8-hour intermittent versus 8-hour continuous exposures. J. Appl. Toxicol. 7: 15–16.

Wilmer, J.W.G.M., R.A. Woutersen, L.M. Appelman, W.R. Leeman and V.J. Feron. 1989. Subchronic (13-week) inhalation toxicity study of formaldehyde in male rats: 8-hour intermittent versus 8-hour continuous exposures. Toxicol. Lett. 47: 287–293.

Witek, T.J., Jr., E.N. Schachter, T. Tosun, G.J. Beck and B.P. Leaderer. 1987. An evaluation of respiratory effects following exposure to 2.0 ppm formaldehyde in asthmatics: lung function, symptoms, and airway reactivity. Arch. Environ. Health 42: 230–237.

Wolverton, B.C., R.C. McDonald and E.A. Watkins, Jr. 1984. Foliage plants for removing indoor air pollutants from energy efficient homes. Econ. Bot. 38: 224–228.

Wortley, P., T.L. Vaughan, S. Davis, M.S. Morgan and D.B. Thomas. 1992. A case–control study of occupational risk factors for laryngeal cancer. Br. J. Ind. Med. 49: 837–844.

Woutersen, R.A., L.M. Appelman, J.W.G.M. Wilmer, H.E. Falke and V.J. Feron. 1987. Subchronic (13-week) inhalation toxicity study of formaldehyde in rats. J. Appl. Toxicol. 7: 43–49.

Woutersen, R.A., A. van Garderen-Hoetmer, J.P. Bruijntjes, A. Zwart and V.J. Feron. 1989. Nasal tumours in rats after severe injury to the nasal mucosa and prolonged exposure to 10 ppm formaldehyde. J. Appl. Toxicol. 9: 39–46.

Yager, J.W., K.L. Cohn, R.C. Spear, J.M. Fisher and L. Morse. 1986. Sister-chromatid exchanges in lymphocytes of anatomy students exposed to formaldehyde-embalming solution. Mutat. Res. 174: 135–139.

Yamada, H. and S. Matsui. 1992. Formation characteristics of formaldehyde and the formaldehyde precursors which release formaldehyde through thermal decomposition in water. Water Sci. Technol. 25(11): 371–378.

Yasuhara, A. and T. Shibamoto. 1995. Quantitative analysis of volatile aldehydes formed from various kinds of fish flesh during heat treatment. J. Agric. Food Chem. 43: 94–97.

Zafiriou, O.C., J. Alford, M. Herrera, E.T. Peltzer, R.B. Gagosian and S.C. Liu. 1980. Formaldehyde in remote marine air and rain: flux measurements and estimates. Geophys. Res. Lett. 7: 341–344.

Zhitkovich, A., A. Lukanova, T. Popov, E. Taioli, H. Cohen, M. Costa and P. Toniolo. 1996. DNA–protein crosslinks in peripheral lymphocytes of individuals exposed to hexavalent chromium compounds. Biomarkers 1: 86–93.

Zhou, X. and K. Mopper. 1990. Apparent partition coefficients of 15 carbonyl compounds between air and seawater and between air and freshwater: Implications for air–sea exchange. Environ. Sci. Technol. 24(12): 1864–1869.

Zimmermann, P.R., R.B. Chatfield, J. Fishman, P.J. Crutzen and P.L. Hanst. 1978. Estimates on the production of CO and H_2 from the oxidation of hydrocarbon emissions from vegetation. Geophys. Res. Lett. 5: 679–682.

Zwart, A., R.A. Woutersen, J.W.G.M. Wilmer, B.J. Spit and V.J. Feron. 1988. Cytotoxic and adaptive effects in rat nasal epithelium after 3-day and 13-week exposure to low concentrations of formaldehyde vapour. Toxicology 51: 87–99.

APPENDIX A SEARCH STRATEGIES EMPLOYED FOR IDENTIFICATION OF RELEVANT DATA

Environmental assessment

Data relevant to the assessment of whether formaldehyde is "toxic" to the environment under CEPA 1999 were identified from original literature, existing review documents, published reference texts and on-line searches conducted between January and May 1996 of the following commercial and government databases: Aqualine (1990–1996), ASFA (Aquatic Sciences and Fisheries Abstracts, Cambridge Scientific Abstracts; 1996), BIOSIS (Biosciences Information Services; 1990–1996), CAB (Commonwealth Agriculture Bureaux; 1990–1996), CESARS (Chemical Evaluation Search and Retrieval System, Ontario Ministry of the Environment and Michigan Department of Natural Resources; 1996), Chemical Abstracts (Chemical Abstracts Service, Columbus, Ohio; 1990–1996), CHRIS (Chemical Hazard Release Information System; 1964–1985), Current Contents (Institute for Scientific Information; 1990–1992, 1996), ELIAS (Environmental Library Integrated Automated System, Environment Canada library; January 1996), Enviroline (R.R. Bowker Publishing Co.; November 1995 – June 1996), Environmental Abstracts (1975 – February 1996), Environmental Bibliography (Environmental Studies Institute, International Academy at Santa Barbara; 1990–1996), GEOREF (Geo Reference Information System, American Geological Institute; 1990–1996), HSDB (Hazardous Substances Data Bank, U.S. National Library of Medicine; 1990–1996), Life Sciences (Cambridge Scientific Abstracts; 1990–1996), NTIS (National Technical Information Service, U.S. Department of Commerce; 1990–1996), Pollution Abstracts (Cambridge Scientific Abstracts, U.S. National Library of Medicine; 1990–1996), POLTOX (Cambridge Scientific Abstracts, U.S. National Library of Medicine; 1990–1995), RTECS (Registry of Toxic Effects of Chemical Substances, U.S. National Institute for Occupational Safety and Health; 1996), Toxline (U.S. National Library of Medicine; 1990–1996), TRI93 (Toxic Chemical Release Inventory, U.S. Environmental Protection Agency, Office of Toxic Substances; 1993), USEPA-ASTER (Assessment Tools for the Evaluation of Risk, U.S. Environmental Protection Agency; up to December 21, 1994), WASTEINFO (Waste Management Information Bureau of the American Energy Agency; 1973 – September 1995) and Water Resources Abstracts (U.S. Geological Survey, U.S. Department of the Interior; 1990–1996). A survey of Canadian industry was carried out under authority of Section 16 of the *Canadian Environmental Protection Act* (CEPA) (Environment Canada, 1997b,c). Targeted companies with commercial activities involving more than 1000 kg of formaldehyde were required to provide information on uses, releases, environmental concentrations, effects or other data that were available to them for formaldehyde. Canadian monitoring data, unpublished reports from Canadian producers and users, and personal communications from experts in the field completed the information consulted in preparing this report. Reveal Alert was used to maintain an ongoing record of the current scientific literature pertaining to the potential environmental effects of formaldehyde. Data obtained after December 1999 were not considered in this assessment unless they were critical data received during the 60-day public review of the report (July 22 to September 20, 2000).

Health assessment

Data relevant to the assessment of the potential risks of formaldehyde to human health were identified through evaluation of existing review documents of the Department of National Health and Welfare (BCH, 1988), the Agency for Toxic Substances and Disease Registry (ATSDR, 1997), the World Health Organization (WHO, 1989), the International Agency for Research on Cancer (IARC, 1995), as well as a review prepared under contract by BIBRA Toxicology International (BIBRA, 1994). To identify additional relevant toxicological data, literature searches on formaldehyde were conducted using the strategy of searching by its name or CAS registry number in the following databases: CCRIS (Chemical Carcinogenesis Research Information System, U.S. National Cancer Institute), DART (Developmental and Reproductive Toxicology, U.S. National Library of Medicine), EMIC (Environmental Mutagen Information Center database, Oak Ridge National Laboratory) and EMICBACK (backfile of EMIC), ETICBACK (backfile of Environmental Teratology Information Center database, U.S. Environmental Protection Agency and U.S. National Institute of Environmental Health Sciences), GENE-TOX (Genetic Toxicology, U.S. Environmental Protection Agency), HSDB, IRIS (Integrated Risk Information System, U.S. Environmental Protection Agency) and RTECS. Its name, registry number and major synonyms were searched in the ToxlinePlus (1985–1999) and Toxline (before 1985) databases. The CAS registry number was searched in the Toxlit (1981–1999) database. The EMBASE (on-line version of Excerpta Medica) database, for 1981–1999, was searched using the name, registry number and major synonyms, combined with a link to toxicological information. In addition to the above sources of information, numerous provincial and federal government officials and representatives of various industrial sectors were contacted between February and August of 1996 for data relevant to exposure and/or effects.

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